Genome-scale regression analysis reveals a linear relationship for promoters and enhancers after combinatorial drug treatment

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Supplementary notes

RNA sample preparation

Human MCF-7 breast cancer cells were purchased from the American Type Culture Collection and maintained in DMEM (Invitrogen) supplemented with 10% FBS containing Penicillin-Streptomycin mixed solution (Nacalai Tesque, Japan). One day before drug treatment, medium was switched to DMEM supplemented with 2% FBS. Cells (approx. 2 x 10^6 cells/sample) were treated separately or in pair-wise combinations with Gefitinib (ZD1839) (1 μM, a generous gift from AstraZeneca), U0126 (500 nM, Calbiochem), and Wortmannin (10 nM, Nacalai Tesque) for six hours. All drugs were dissolved in DMSO and DMSO was used as the treatment control. After the treatment, the cells were washed with PBS twice followed by RNA purification using the miRNeasy Mini kit (QIAGEN) and quality check using Bioanalyzer (Agilent technology).

Single molecule CAGE data production

Triplicate samples were analyzed for each drug treatment. CAGE libraries for single molecule sequencing were constructed using 5 μg of total RNA as described previously (Kanamori-Katayama et al., 2011), and sequenced on HeliScope. CAGE tags were processed and mapped to genomic positions as described in detail in (Kajiyama et al., 2013). Briefly, tags remaining after filtering of low quality and ribosomal tags were mapped to the human genome (hg19) using Delve.

CAGE promoter and enhancer expression normalization and differential expression analysis

Mapped CAGE tags were projected onto FANTOM 5 pre-defined robust decomposition peak identification (DPI) cluster regions of promoters and enhancers (Forrest et al., 2014; Andersson et al., 2014; Arner et al., 2015) by the intersectBed function of bedtools (Quinlan, 2014) with default parameters. Expression tables were normalized by the "Relative Log Expression" (RLE) method.
as implemented in edgeR (Robinson et al., 2010). Lowly expressed tag clusters were subsequently removed and we kept only tag clusters expressed more than five counts per million (CPM) in at least one sample from the RLE-normalized expression for promoters and more than five counts in at least twelve samples from the RLE-normalized expression for enhancers. In addition, the voom transformation was performed to adjust CPM values to fit a normal distribution by limma (Diboun et al., 2006). We used negative binomial generalized linear models (GLM) for differential analysis of promoters (McCarthy et al., 2012). A GLM likelihood ratio test was applied to identify the significantly altered promoters of treatment conditions against the control condition. The p-values for differential expression were adjusted for multiple testing using false discovery rate (FDR) < 0.05 as a threshold for statistical significance.

**Alternative regression models**

**Quantile Regression:** Ordinary least-squares linear regression models the relationship between predictor variables and the conditional mean of the response variable for given levels of the predictor variables. Quantile regression models the relationship between predictor variables and the conditional quantiles of the response variable for given levels of the predictor variables (Koenker, Roger, 1978). All the models were evaluated using ten-fold cross validation. We used 'quanteg' R package for fitting the models (Koenker). We firstly applied quantile regression using the median (Quantile regression=0.5). We also performed internal cross-validation (we kept one fold for validation) to find the quantile that maximizes the Pearson correlation coefficient in the validation set. The results shown in Supplementary Tables 5-7 are the mean performance after ten-fold cross-validation in the test set.

**Regression Tree:** Linear regression is a global model, where there is an only one predictive function holding over the whole data-space. However if the independent variables interact in nonlinear ways, one simple approach would be to partition the space into smaller regions and fit a different model for each partition. Regression trees are used to represent the recursive partitioning. We used 'tree' R package for fitting the regression tree (Ripley). We optimized the within-node deviance parameter (mindev) using internal cross-validation. The results shown in Supplementary Tables 5-7 are the mean performance after ten-fold cross-validation in the test set.

**Linear regression using one predictor variable:** We further tried to fit the linear regression model using only the dominant drug profile as input variable. The results shown in Supplementary Tables 5-7 are the mean performance after ten-fold cross-validation in the test set.

**Multivariable linear regression with interaction term:** We also fit the full model with the two drug profiles as input variables plus a term for their pairwise interaction. The results shown in Supplementary Tables 5-7 are the mean performance after ten-fold cross-validation in the test set.

We further tested whether the performance of the alternative regression models is significantly different than the performance of multivariable linear regression (two explanatory variables). After we performed an F-test to compare whether the variances of samples are equal (p-value>0.05 in all
comparisons), we performed two-sample t-tests for equal means and confidence level 95%, contrasting the 10-fold Pearson correlation coefficients of multivariable linear regression with the 10-fold Pearson correlation coefficients achieved by the alternative models. The exact p-values of the tests are illustrated in Supplementary Tables 5-7 for all drug pairs. As we can notice there is no statically significant difference between multivariable linear regression, quantile regression, and multivariable linear regression with interaction term and moreover, the multivariable linear regression outperforms simple linear regression and regression tree.

Evaluation Metrics

To evaluate the robustness and prediction ability of the regression models on new unseen values of the response variable, we performed 10-fold cross validation. We used three different metrics to assess the performance of the regression models on the test set.

Mean Absolute Error (MAE): measures the average magnitude of the errors in a set of predictions.

$$\text{MAE} = \frac{1}{n} \sum_{i=1}^{n} |y(i) - \hat{y}(i)|$$

where $y(i)$ is the observed value, $\hat{y}(i)$ is the predicted value, and $n$ equals the number of observations in the test set.

Pearson Correlation Coefficient: measures the linear correlation between paired variables.

$$r = \frac{n(\Sigma y_i \hat{y}_i) - \Sigma y_i \Sigma \hat{y}_i}{\sqrt{n[\Sigma y_i^2 - (\Sigma y_i)^2][\Sigma \hat{y}_i^2 - (\Sigma \hat{y}_i)^2]}}$$

where $y_i$ and $\hat{y}_i$ are the observed and the predicted value respectively for $i=1, 2, \ldots n$, and $n$ is the total number of observations in the test set.

Spearman correlation coefficient: measures the strength of a monotonic relationship between paired variables. It is defined as the Pearson’s correlation on the ranked variables.

$$r_s = 1 - \frac{6 \Sigma d_i}{n(n^2-1)}$$

where $d_i = \text{rg}(y_i) - \text{rg}(\hat{y}_i)$ is the difference between the two ranks of each observation and $n$ is the total number of observations in the test set.
**Action of the Gefitinib, Wortmannin, and U0126**

Gefitinib inhibits EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme (Wakeling et al., 2002). EGFR lies upstream of the Ras-ERK and PI3K-Akt pathways. U0126 is a highly selective inhibitor of MEK1 and MEK2 kinases (Duncia et al., 1998), while Wortmannin is a fungal metabolite that acts as a potent, irreversible inhibitor of phosphatidylinositol 3-kinase (PI3K) (Powis et al., 1994). The composite effects of the three compounds have been previously reported in the literature. Gefitinib and U0126 mixture inhibits the growth of RAS-active cancer cells (El-Chaar et al., 2014). Gefitinib in combination with Wortmannin suspends proliferation of U87 cells, compared to the individual drugs alone (Yelskaya et al., 2013) while U0126 and Wortmannin jointly lead to synergistic induction of apoptosis in LN215 and LN229 cell lines (Failly et al., 2007).

**Permutation tests**

To validate the statistical significance of the results and test whether both drug conditions contribute to the model, we performed the same regression analysis 100,000 times with random permutations of one of the single drug treatment profiles. The Pearson correlation between the observed and predicted values after the permutations was significantly lower for all combinations (p-value < 2.2e-16) compared to the regression model based on the non-permuted individual drug profiles (Supplementary Figure 3 and 6 for promoters and enhancers respectively).

**Promoters that do not follow the global linear trend**

To identify the promoters that were not described efficiently by the linear regression function, we examined the distribution of residuals. We selected all the promoters, which fell further than two standard deviations away from what would have been expected based on the regression model and compared to the set of differentially expressed ones (Supplementary Figure 9).

**Gene Ontology enrichment of promoters not described by the linear model**

To gain further insight into this group of promoters and investigate whether there is any distinct pattern that characterizes them, we performed a multiple step analysis. The non-linearly described promoters were subjected to Gene Ontology (Ashburner et al., 2000) enrichment analysis (Supplementary Tables 10-17). In the Molecular Function ontology, out of the model promoters in all drug combinations were highly enriched with "RNA polymerase II transcription factor activity"
and "nucleic acid binding transcription factor activity" terms, suggesting that transcription factors are abundant among the promoters that do not behave linearly (Supplementary Figure 10).

We used only promoters which have been associated with Entrez Gene IDs. We ran the topGO R package (topGO: Enrichment Analysis for Gene Ontology. R package version 2.24.0.) for gene ontology enrichment analysis (algorithm = "classic", statistic = "fisher", genes of interest: genes associated with the non-linearly behaved promoters, background genes: genes associated with all the promoters in the study). We applied the Benjamini-Hochberg (BH) adjustment of the p-values. The analysis yielded no significantly enriched GO terms for the Cellular Component domain for the Gefitinib-Wortmannin drug combination. We then used REVIGO software (Supek et al., 2011) to summarize and cluster the enriched Gene Ontology terms based on semantic similarity (Allowed similarity=0.7).

The ratio of transcription factors in the non-well explained promoters (11.3% for Gefitinib-U0126, 11.4% for Gefitinib-Wortmannin, 13.2% for U0126-Wortmannin) was higher than the ratio of the transcription factors in the well-described promoters (9.7% for Gefitinib-U0126, 9.7% for Gefitinib-Wortmannin, 9.6% for U0126-Wortmannin) for all drug combinations, with statistically significant difference (Fisher's exact test, conf.level = 0.95) for the U0126-Wortmannin pair (p-value=0.005695). We also checked whether the promoters of the transcription factors were lowly expressed compared to all the promoters of our analysis. The distribution of the expression (median log2cpm values across all the samples) in these two sets suggests that our findings are not due to low expression of transcription factors. However the transcription factors in the linearly described promoters have higher expression than the transcription factors in the non-linearly described promoters (Supplementary Figure 11).

**Transcription factor binding site analysis of promoters not described by the linear model**

We further identified conserved transcription factor DNA binding sites (TFBSs) in the promoter regions. Overrepresented motifs in non-linearly described promoters for every combinatorial treatment were identified using the Binomial test (Supplementary Tables 18-20). Several motifs overrepresented in promoters not described by the linear model were common to all drug combinations, and are listed in Supplementary Table 21. Redoing the analysis excluding promoters overlapping between drug combinations suggested that these common motifs were due to the common promoter regions in the three drug combinations.

Potential transcription factor binding sites (TFBSs) for motifs known to be recognized by transcription factors (TFs) were identified as described in detail in (Arner et al., 2015). Briefly, MotEvo (Arnold et al., 2012) was used to identify conserved instances of motifs from the SwissRegulon database (Pachkov et al., 2007) within a 400 base region (-300 to +100 base pairs with respect to the representative position) of each promoter. Overrepresented motifs in non-linearly behaved promoters for every combinatorial treatment were realized using one-tailed Binomial test (alternative: "greater", number of successes: number of occurrences of a motif in the
non-linearly described promoters, number of trials: number of the non-linearly described promoters, background probability: number of occurrences of a motif in all the promoters divided by the number of all the promoters). Then we applied the Benjamini-Hochberg (BH) adjustment of the p-values.
Supplementary Figures
Supplementary Figure 1: Scatter plots of promoter expression (log$_{2}$cpm) among triplicates. The high Pearson correlation denotes that the quantification of the transcriptome by the HeliScopeCAGE method is reproducible even in a low-dosage drug experiment.
Supplementary Figure 2: Scatter plots of observed versus predicted log2FC values for A) Gefitinib_U0126, B) Gefitinib-Wortmannin and C) U0126-Wortmannin drug combination. Blue dots indicate promoters differentially expressed both in single and combinatorial treatment, red dots denote promoters differentially expressed only in combinatorial treatment and gray dots represent the non-significantly altered promoters. The dashed lines define the bounds for the two standard deviations of the residual error. Barplots show the expression of key genes important for the phenotypic outcome after single and combinatorial treatment. The linear regression model is able to effectively capture both amplifications and cancellations of the combinatorial transcriptome response.
Supplementary Figure 3: Density plots of the Pearson correlation coefficients between observed and predicted values after the permutations of individual profiles for (A) Gefitinib_U0126, (B) Gefitinib_Wortmannin, and (C) U0126_Wortmannin drug combinations in promoters. The Pearson correlation coefficient achieved without permutation is also reported.
Supplementary Figure 4: Scatter plots of enhancers’ expression (log_{2}cpm) among triplicates after filtering. The mean Pearson among triplicates is 0.74.
Supplementary Figure 5: PCA plot of enhancer activities. Colors represent different treatments individually or in combination, with squares indicating control (DMSO) treatment, circles indicating individual drug treatment and triangles indicating combinatorial treatment.
Supplementary Figure 6: Density plots of the Pearson correlation coefficients between observed and predicted values after the permutations of individual profiles for (a) Gefitinib_U0126, (b) Gefitinib_Wortmannin, and (c) U0126_Wortmannin drug combinations in enhancers. The Pearson correlation coefficient achieved without permutation is also reported.
Supplementary Figure 7: Distinct effects of single and combinatorial therapy on different promoter elements of the same gene. A) FAM110A gene, an uncharacterized protein-coding gene mainly expressed in blood cells, has two different promoters upregulated by Gefitinib-Wortmannin combinatorial treatment. The first promoter (p1@FAM110A) is upregulated mainly because of the effect of Wortmannin and to a lesser extent because of Gefitinib. On the other hand, Wortmannin did not change the expression of the other promoter (p3@FAM110A), which was upregulated by Gefitinib treatment only. B) Zenbu Genome browser view of CAGE promoters p1 and p3. These two promoters are widely separated (10875 bp) and have a completely different set of transcription factor binding sites (noted in brackets). C) The same pattern is observed in U0126-Wortmannin combinatorial treatment. Wortmannin again plays the dominant role in the upregulation of p1@FAM110A but has no effect on the expression of p3@FAM110A. In contrast, U0126 clearly upregulates the p3@FAM110A promoter in the U0126-Wortmannin combination. Bar plots show the expression of promoters p1 (right panel) and p3 (left panel) of FAM110A gene, in the control condition, after single and combinatorial drug treatments. Above each bar, the p-value of the differential expression analysis of the corresponding treatment is reported (McCarthy et al., 2012). Asterisks indicate the statistical significant upregulated therapies after FDR correction.
Supplementary Figure 8: We sampled 1028 low expressed promoter 10000 times, and applied linear regression for the three drug pairs. The density plots of the Pearson correlation between observed and estimated combinatorial response which we obtained after down sampling of promoters are presented in A) for Gefitinib-U0126, B) Gefitinib-Wortmannin and C) U0126-Wortmannin drug pairs. The red line denotes the Pearson correlation coefficient achieved for all the promoters while the black line indicates the Pearson correlation coefficient achieved for enhancers. The results suggest that the lower performance of the linear regression in enhancers compared to promoters can be attributed to the appreciably lower expression of eRNAs since the performance of the low expressed promoters decreased to almost the same levels as the performance in enhancers. The correlation between estimated and observed transcriptional response of all the promoters is higher than the mean of correlations obtained after down sampling, by 8.15, 5.38 and 4.55 standard deviations for Gefitinib-U0126, Gefitinib-Wortmannin, and U0126-Wortmannin combinations respectively.
Supplementary Figure 9: A) Multivariable regression model with two explanatory variables fits a regression plane in 3-dimensional space. Red dots represent promoters which fall further than two standard deviations away from what would have been expected based on the regression surface. B) Distribution of the residuals for Gefitinib_U0126 regression model. Composition of the “non-linearly described” promoters for the C) Gefitinib_U0126, D) Gefitinib_Wortmannin and E) U0126_Wortmannin combinatorial treatment. Using linear regression, it is possible to explain the response of 2963 out of 3256 (91%) promoters significantly differentially expressed by combinatorial treatment only for the Gefitinib-U0126 drug pair (85% and 80% respectively for the Gefitinib-Wortmannin and U0126-Wortmannin combinations). F) Overlap of the “out of the model” promoters among the three different drug combinations is small, with only 58 promoters in common.
Supplementary Figure 10: Gene Ontology enrichment analysis for the promoters that do not follow the global linear trend. Molecular Function enrichment analysis visualized as an MDS plot, using REVIGO software (Supek et al., 2011) (Allowed similarity=0.7) in (A) Gefitinib-U0126 (B) Gefitinib-Wortmannin and (C) U0126-Wortmannin combinatorial drug treatments. Clusters of circles represent terms that are closely related. Circle color indicates the log10 p-value of the enrichment test while circle size indicates the frequency of the GO term in the Uniprot database.
Supplementary Figure 11: Box plots of the expression (median log2 cpm values across all the samples) in A) all the promoters of our analysis and only in the promoters of transcription factors (TFs). TF promoters as a whole do not have substantially lower expression than the whole promoter set. However the TFs in the linearly described promoters have higher expression than the TFs in the non-linearly described promoters for the B) Gefitinib-U0126, C) Gefitinib-Wortmannin and D) U0126-Wortmannin drug combination. The p-values of two sample Wilcoxon test comparing the expression of TF promoters which are well explained by the linear model versus the expression of TF promoters not well explained by the linear model are also reported.
Table 1: Promoters of phenotypically important genes (obtained from UniProtKB and (Sjoblom et al., 2006)) which are well described by the linear regression model (within two standard deviations of the residual error) and are strongly regulated in Gefitinib-U0126 combinatorial treatment. For every promoter, the log_{2} FC expression values of combinatorial and single drug treatments compared to control, the residual error and the phenotype category are given.

| Promoters | Gefitinib_U0126 (log_{2}FC) | Gefitinib (log_{2}FC) | U0126 (log_{2}FC) | Residuals | Category |
|-----------|-----------------------------|-----------------------|-------------------|-----------|----------|
| p1@NCOA4  | 0.334646                    | 0.101528              | 0.16021           | 0.14927   | oncogene |
| p2@NCOA4  | 0.375721                    | 0.179023              | 0.262725          | 0.06864   | oncogene |
| p2@CCDC6  | -0.39564                    | 0.067342              | -0.19835          | -0.22878  | oncogene |
| p3@CCDC6  | -0.48386                    | -0.30512              | -0.4398           | 0.028544  | oncogene |
| p2@CCND1  | -0.60879                    | -0.55169              | -0.234            | -0.21603  | oncogene |
| p1@PICALM | -0.26796                    | -0.09458              | -0.16705          | -0.08072  | oncogene |
| p1@DDIT3  | 0.283415                    | 0.158984              | 0.046417          | 0.18865   | oncogene |
| p2@MDM2   | 0.206962                    | 0.110179              | 0.175325          | 0.004503  | oncogene |
| p1@CDT1   | -0.30058                    | -0.00455              | -0.27401          | -0.03933  | oncogene |
| p1@ELAC2  | 0.230876                    | 0.009271              | 0.114724          | 0.117443  | oncogene |
| p2@YES1   | -0.43229                    | -0.37158              | -0.36677          | 0.031132  | oncogene |
| p1@TPM3   | -0.39032                    | 0.039099              | -0.18468          | -0.22772  | oncogene |
| p1@PBX1   | -0.35289                    | -0.08869              | -0.14964          | -0.18406  | oncogene |
| p1@TOP1   | -0.39188                    | -0.15936              | -0.19931          | -0.15382  | oncogene |
| p2@TOP1   | -0.31106                    | -0.07869              | -0.21251          | -0.08542  | oncogene |
| p1@AURKA  | 0.261269                    | 0.17893               | 0.112259          | 0.097584  | oncogene |
| p1@RUNX1  | -0.48457                    | -0.17984              | -0.1768           | -0.26161  | oncogene |
| p5@RUNX1  | -0.53647                    | -0.07012              | -0.29899          | -0.23109  | oncogene |
| p1@EWSR1  | -0.19071                    | -0.13414              | -0.12518          | -0.0311   | oncogene |
| p1@MKL1   | -0.31867                    | -0.24674              | -0.05564          | -0.1904   | oncogene |
| p1@PIM3   | 0.323689                    | 0.108056              | 0.120917          | 0.173728  | oncogene |
| p1@TSG    | 0.276067                    | -0.02285              | 0.124536          | 0.163243  | oncogene |
| p1@WWTR1  | 0.261255                    | 0.209425              | 0.102207          | 0.097693  | oncogene |
| p1@RHOA   | 0.199587                    | 0.093437              | 0.041945          | 0.129405  | oncogene |
| p4@AFF1   | -0.54389                    | -0.20105              | -0.40415          | -0.09772  | oncogene |
| p3@AFF4   | -0.21215                    | -0.01076              | -0.07255          | -0.14093  | oncogene |
| Gene          | p-value1 | p-value2 | p-value3 | p-value4 | Class          |
|--------------|----------|----------|----------|----------|----------------|
| p1@FOXO3     | 0.380783 | 0.407646 | 0.108792 | 0.149492 | oncogene       |
| p1@MYB       | -0.34534 | -0.09502 | -0.22305 | -0.1046  | oncogene       |
| p1@FAM83B    | 0.217532 | 0.121525 | 0.140818 | 0.044433 | oncogene       |
| p1@CREB3L2   | 0.288149 | 0.114077 | 0.198462 | 0.062434 | oncogene       |
| p1@MYC       | -0.41929 | -0.1079  | -0.21317 | -0.18397 | oncogene       |
| p1@PCMI1     | -0.36932 | -0.17367 | -0.241   | -0.08709 | oncogene       |
| p15@SET      | -0.34378 | -0.03091 | -0.22448 | -0.12156 | oncogene       |
| p1@JAK2      | 0.351242 | 0.274533 | 0.269381 | 0.008207 | oncogene       |
| p1@MTCP1     | -0.38249 | -0.15481 | -0.25555 | -0.09225 | oncogene       |
| p1@ZMYND11   | -0.36573 | -0.04537 | -0.06103 | -0.29475 | tumor suppressor|
| p2@HTATIP2   | 0.607389 | 0.414589 | 0.284422 | 0.206601 | tumor suppressor|
| p2@EXT2      | 0.943464 | 0.54377  | 0.630427 | 0.172942 | tumor suppressor|
| p1@EXT2      | 0.300974 | -0.06026 | 0.207477 | 0.120722 | tumor suppressor|
| p1@BRMS1     | -0.31984 | -0.13116 | -0.11841 | -0.1676  | tumor suppressor|
| p1@TCHP      | -0.36608 | -0.14912 | -0.24758 | -0.08519 | tumor suppressor|
| p1@CDKN1B    | 0.316064 | 0.180056 | 0.090772 | 0.172503 | tumor suppressor|
| p1@GPRC5A    | 0.270881 | 0.007319 | 0.140064 | 0.133908 | tumor suppressor|
| p1@BRCA2     | -0.36526 | -0.11501 | -0.21805 | -0.12309 | tumor suppressor|
| p4@STARD13   | -0.20186 | -0.20114 | -0.06211 | -0.08157 | tumor suppressor|
| p1@PNN       | -0.23177 | -0.12075 | -0.07594 | -0.12322 | tumor suppressor|
| p1@BUB1B     | -0.52247 | -0.19674 | -0.23672 | -0.23716 | tumor suppressor|
| p1@PALB2     | -0.2788  | -0.0749  | -0.16455 | -0.10005 | tumor suppressor|
| p1@PYCARD    | 0.252434 | 0.12689  | 0.180992 | 0.039393 | tumor suppressor|
| p1@BRD7      | -0.3299  | -0.06879 | -0.13783 | -0.17849 | tumor suppressor|
| p1@CYLD      | 0.369011 | 0.002177 | 0.189655 | 0.186381 | tumor suppressor|
| p2@RBL2      | 0.559558 | 0.289622 | 0.373774 | 0.112377 | tumor suppressor|
| p1@CTCF      | -0.22722 | -0.08612 | -0.0513  | -0.15288 | tumor suppressor|
| p2@CTCF      | -0.56382 | -0.23981 | -0.32931 | -0.17694 | tumor suppressor|
| p1@PHLPP2    | -0.44917 | -0.21659 | -0.23259 | -0.16166 | tumor suppressor|
| p3@NF1       | -0.59506 | -0.19513 | -0.26022 | -0.28787 | tumor suppressor|
| p1@TXNIP     | 0.330836 | 0.11937  | 0.202587 | 0.09955  | tumor suppressor|
| Gene       | Value1   | Value2   | Value3   | Value4   | Description          |
|------------|----------|----------|----------|----------|----------------------|
| p1@CDC73  | -0.27483 | -0.00609 | -0.15283 | -0.12857 | tumor suppressor     |
| p2@CDC73  | -0.29258 | -0.1642  | -0.19271 | -0.05931 | tumor suppressor     |
| p1@RBL1   | -0.45326 | -0.19564 | -0.17399 | -0.22802 | tumor suppressor     |
| p1@CHEK2  | -0.24367 | -0.14443 | -0.15533 | -0.05213 | tumor suppressor     |
| p1@TMEM127| 0.377517 | 0.178951 | 0.149488 | 0.178353 | tumor suppressor     |
| p1@TET2   | -0.5506  | -0.2626  | -0.32493 | -0.16083 | tumor suppressor     |
| p1@SDHA   | 0.184283 | -0.065   | 0.051995 | 0.153645 | tumor suppressor     |
| p2@TRIM24 | 0.372905 | 0.401095 | 0.145055 | 0.109092 | tumor suppressor     |
| p1@RBMX   | 0.458237 | 0.335962 | 0.185055 | 0.176505 | tumor suppressor     |
| p1@SBNO1  | -0.21919 | -0.08869 | -0.10892 | -0.08916 | breast cancer gene   |
| p3@THBS3  | -0.49564 | -0.1421  | -0.14739 | -0.31239 | breast cancer gene   |
| p1@MACF1  | -0.47446 | -0.24776 | -0.27212 | -0.13961 | breast cancer gene   |
| p1@SULF2  | -0.33701 | -0.28864 | -0.2358  | -0.02409 | breast cancer gene   |
| p2@SULF2  | -0.29708 | -0.14802 | -0.15592 | -0.10388 | breast cancer gene   |
| p3@SULF2  | -0.37175 | -0.41333 | -0.25783 | 0.000812 | breast cancer gene   |
| p4@SULF2  | -0.26054 | -0.29724 | -0.29449 | 0.110961 | breast cancer gene   |
| p1@ZFP64  | -0.32782 | -0.12554 | -0.1973  | -0.10216 | breast cancer gene   |
| p1@SLC9A2 | 0.577064 | 0.229123 | 0.270715 | 0.246838 | breast cancer gene   |
| p2@RAPH1  | -0.38208 | -0.18156 | -0.15832 | -0.17619 | breast cancer gene   |
| p3@RAPH1  | -0.43375 | -0.14494 | -0.18692 | -0.21196 | breast cancer gene   |
| p3@LRRFIP1| -0.3202  | -0.08647 | -0.27991 | -0.02793 | breast cancer gene   |
| p1@GAB1   | -0.56814 | 0.039318 | -0.49332 | -0.11153 | breast cancer gene   |
| p1@DBN1   | 0.243235 | 0.052843 | 0.128279 | 0.103377 | breast cancer gene   |
| p1@PRPF4B | -0.25406 | -0.16341 | -0.07098 | -0.13701 | breast cancer gene   |
| p1@GSN    | 0.393441 | 0.180389 | 0.174745 | 0.169766 | breast cancer gene   |
| p2@GSN    | 0.460701 | 0.228113 | 0.185942 | 0.21156  | breast cancer gene   |
Supplementary Table 2: Promoters of phenotypically important genes (obtained from UniProtKB and (Sjoblom et al., 2006)) which are well described by the linear regression model (within two standard deviations of the residual error) and are strongly regulated in Gefitinib-Wortmannin combinatorial treatment. For every promoter, the log(FC) expression values of combinatorial and single drug treatments compared to control, the residual error and the phenotype category are given.

| Genes  | Gefitinib-Wortmannin (log(FC)) | Gefitinib (log(FC)) | Wortmannin (log(FC)) | Residuals | Category |
|--------|--------------------------------|---------------------|----------------------|-----------|----------|
| p2@CCDC6 | -0.42939 | 0.067342 | -0.17399 | -0.33732 | oncogene |
| p2@PICALM | -0.4352 | -0.02888 | -0.36805 | -0.18404 | oncogene |
| p1@DDIT3 | 0.335786 | 0.158984 | 0.232598 | 0.12793 | oncogene |
| p1@MDM2 | 0.217063 | 0.028296 | 0.07757 | 0.15264 | oncogene |
| p1@AKT1 | -0.24623 | -0.08105 | -0.09499 | -0.16197 | oncogene |
| p3@CBFB | -0.70006 | -0.54108 | -0.52787 | -0.18641 | oncogene |
| p1@SPECC1 | -0.23934 | -0.02203 | -0.07321 | -0.18757 | oncogene |
| p2@YESI | -0.41219 | -0.37158 | -0.30901 | -0.09647 | oncogene |
| p1@PRKACA | -0.21538 | -0.03295 | -0.19493 | -0.07885 | oncogene |
| p3@TPM3 | -0.40849 | -0.02588 | -0.19222 | -0.27591 | oncogene |
| p1@TPM3 | -0.35494 | 0.039099 | -0.22779 | -0.21829 | oncogene |
| p1@TOP1 | -0.33918 | -0.15936 | -0.22083 | -0.14692 | oncogene |
| p2@TOP1 | -0.35755 | -0.07869 | -0.19373 | -0.20793 | oncogene |
| p53@GNAS | 0.527622 | 0.216335 | 0.408416 | 0.184689 | oncogene |
| p1@RUNX1 | -0.35714 | -0.17984 | -0.03632 | -0.28214 | oncogene |
| p1@TGF | 0.215109 | -0.02285 | 0.128822 | 0.131916 | oncogene |
| p1@AFF1 | -0.537111 | -0.23853 | -0.2673 | -0.28972 | oncogene |
| p4@AFF1 | -0.54127 | -0.20105 | -0.51945 | -0.13651 | oncogene |
| p1@FER | -0.3699 | -0.16825 | -0.22881 | -0.1696 | oncogene |
| p1@DEK | -0.32006 | -0.08593 | -0.16852 | -0.18511 | oncogene |
| p7@SET | -0.63292 | -0.42666 | -0.46163 | -0.19835 | oncogene |
| p1@JAK2 | 0.333681 | 0.274533 | 0.175511 | 0.128943 | oncogene |
| p1@BRMS1 | -0.26168 | -0.13116 | -0.15457 | -0.12233 | tumor suppressor |
| p1@ING4 | 0.337535 | 0.167189 | 0.037327 | 0.257869 | tumor suppressor |
| p1@BRCA2 | -0.4 | -0.11501 | -0.23323 | -0.21291 | tumor suppressor |
| p1@BUB1B | -0.53497 | -0.19674 | -0.26058 | -0.30476 | tumor suppressor |
| p1@PYCARD | 0.253342 | 0.12689 | 0.173073 | 0.095067 | tumor suppressor |
| p1@PHLPP2 | -0.40329 | -0.21659 | -0.07728 | -0.28973 | tumor suppressor |
| p3@NF1 | -0.45166 | -0.19513 | -0.2436 | -0.2333 | tumor suppressor |
| p1@PAF1 | -0.257 | 0.035183 | -0.14255 | -0.1762 | tumor suppressor |
| p2@EFNA1 | 0.642197 | 0.220102 | 0.363328 | 0.328294 | tumor suppressor |
| p1@FH | -0.24949 | -0.19239 | -0.1462 | -0.09714 | tumor suppressor |
| p1@TMEM127 | 0.300896 | 0.178951 | 0.197182 | 0.110679 | tumor suppressor |
| p1@PRKCD | 0.406829 | 0.270667 | 0.107057 | 0.249077 | tumor suppressor |
| p1@TET2 | -0.4004 | -0.2626 | -0.11642 | -0.24666 | tumor suppressor |
| p1@PLK2 | -0.24721 | -0.07303 | 0.087122 | -0.28726 | tumor suppressor |
| p1@RASA1 | 0.245191 | 0.098157 | 0.044698 | 0.181554 | tumor suppressor |
| p1@UFL1 | 0.208436 | 0.08148 | 0.126871 | 0.094871 | tumor suppressor |
| Gene     | Value1    | Value2    | Value3    | Value4    |
|----------|-----------|-----------|-----------|-----------|
| p1@AMFR  | 0.259775  | 0.109864  | 0.117867  | 0.143617  |
| p1@SULF2 | -0.35762  | -0.28864  | -0.28104  | -0.08581  |
| p2@SULF2 | -0.23624  | -0.14802  | -0.18114  | -0.07399  |
| p3@RAPH1 | -0.31157  | -0.14494  | -0.151    | -0.17042  |
| p1@LRRFIP1| -0.24921  | -0.00237  | -0.08696  | -0.19421  |
| p3@LRRFIP1| -0.35546  | -0.08647  | -0.13657  | -0.24173  |
| p1@HDLBP | 0.209796  | 0.182969  | 0.156101  | 0.045852  |
| p2@HDLBP | 0.205334  | 0.055827  | 0.199532  | 0.050931  |

breast cancer gene
Supplementary Table 3: Promoters of phenotypically important genes (obtained from UniProtKB and (Sjoblom et al., 2006)) which are well described by the linear regression model (within two standard deviations of the residual error) and are strongly regulated in U0126-Wortmannin combinatorial treatment. For every promoter, the log2FC expression values of combinatorial and single drug treatments compared to control, the residual error and the phenotype category are given.

| Genes      | U0126    | Wortmannin | Residuals | Category       |
|------------|----------|------------|-----------|----------------|
|            |(log2 FC) | (log2 FC)  |           |                |
| p2@MXI1    | 0.369284 | 0.155083   | 0.242662  | 0.203165       |
| p3@CCDC6   | -0.42874 | -0.4398    | -0.23299  | -0.09896       |
| p1@LETMD1  | 0.189006 | 0.072418   | 0.070623  | 0.124101       |
| p3@BCAS4   | 0.461749 | 0.172736   | 0.29642   | 0.268826       |
| p2@BCAS4   | 0.298246 | 0.131069   | -0.01283  | 0.224194       |
| p1@PIM3    | 0.380252 | 0.120917   | 0.219632  | 0.241306       |
| p1@WWTR1   | 0.268747 | 0.102207   | 0.224637  | 0.139311       |
| p1@DCUN1D1 | -0.34976 | -0.14128   | 0.058468  | -0.28492       |
| p1@TCTA    | 0.262496 | 0.106377   | 0.182333  | 0.1435         |
| p1@CREB3L2 | 0.359336 | 0.198462   | 0.218126  | 0.175113       |
| p1@AGR2    | -0.23613 | -0.00382   | 0.089691  | -0.26189       |
| p1@JAK2    | 0.299522 | 0.269381   | 0.175511  | 0.086465       |
| p1@BRCA2   | -0.42488 | -0.21805   | -0.23323  | -0.22581       |
| p1@BUB1B   | -0.39667 | -0.23672   | -0.26058  | -0.17824       |
| p3@NF1     | -0.48958 | -0.26022   | -0.2436   | -0.26248       |
| p2@NBL1    | -0.24321 | -0.10373   | -0.07815  | -0.15886       |
| p1@CHEK2   | -0.22753 | -0.15333   | -0.11751  | -0.10074       |
| p1@TET2    | -0.46096 | -0.32493   | -0.11642  | -0.23447       |
| p1@DLC1    | 0.308235 | 0.205354   | 0.168449  | 0.135094       |
| p2@EPB49   | 0.394629 | 0.267418   | 0.219693  | 0.169257       |
| p1@KTN1    | -0.34987 | -0.09855   | -0.19245  | -0.23372       |
| p10@SULF2  | -0.34297 | -0.17647   | -0.27568  | -0.15548       |
| p1@KPNA5   | -0.36321 | -0.14653   | -0.27798  | -0.19268       |
Supplementary Table 4: For every combinatorial treatment in promoters, we report the permuted drug profile, the coefficient of this profile in the linear prediction function, the p-value of one sample t-test comparing the Pearson correlation of the regression model with the Pearson coefficients obtained after permutations of drug profile (assuming approximately Gaussian distributions, null hypothesis: mean of correlation coefficients of the permuted profile is equal to the correlation of the regression model, confidence level: 95%), and the number of the standard deviations which the correlation of the regression model based on the non-permutated drug expression is higher than the mean of correlation coefficients obtained using the permuted drug profile.

| Drug Combination       | Permuted Drug | Coefficient | p-value    | No.of.sd | Permuted Drug | Coefficient | p-value    | No.of.sd |
|------------------------|---------------|-------------|------------|----------|---------------|-------------|------------|----------|
| Gefitinib-U0126        | Gefitinib     | 0.310036    | <2.2e-16   | 1073.51  | U0126         | 0.952823    | <2.2e-16   | 5020.19  |
| Gefitinib-Wortmannin   | Gefitinib     | 0.303648    | <2.2e-16   | 858.32   | Wortmannin    | 0.669232    | <2.2e-16   | 3103.47  |
| U0126-Wortmannin       | U0126         | 0.589808    | <2.2e-16   | 2943.02  | Wortmannin    | 0.304918    | <2.2e-16   | 1096.52  |
Supplementary Table 5: Performance of the different regression models for the Gefitinib-U0126 drug combination. The p-values of two sample t-test comparing the performance of each model with multivariable linear regression (2 explanatory variables) are also reported.

| Model                                      | Mean Absolute Error | Pearson correlation | Spearman correlation | P-Value     |
|--------------------------------------------|---------------------|---------------------|----------------------|-------------|
| Linear regression (2 explanatory variables)| 0.1160              | 0.8418              | 0.8284               | -           |
| Linear regression (1 explanatory variables)| 0.1216              | 0.8233              | 0.8071               | 0.0003197   |
| Linear regression (2 explanatory variables plus interaction term) | 0.1160              | 0.8415              | 0.8284               | 0.9449      |
| Quantile regression (0.5 quantile)        | 0.1158              | 0.8418              | 0.8281               | 0.9867      |
| Quantile regression (0.35 quantile)       | 0.1234              | 0.8418              | 0.8283               | 0.9963      |
| Regression tree                            | 0.1190              | 0.8294              | 0.8214               | 0.01836     |
**Supplementary Table 6:** Performance of the different regression models for the Gefitinib-Wortmannin drug combination. The p-values of two sample t-test comparing the performance of each model with multivariable linear regression (2 explanatory variables) are also reported.

| Model                          | Mean Absolute Error | Pearson correlation | Spearman correlation | P-Value |
|-------------------------------|---------------------|---------------------|----------------------|---------|
| Linear regression (2 explanatory variables) | 0.1238              | 0.7453              | 0.7474               | -       |
| Linear regression (1 explanatory variable) | 0.1285              | 0.7202              | 0.7173               | 0.0002241 |
| Linear regression (2 explanatory variables plus interaction term) | 0.1236              | 0.7447              | 0.7475               | 0.9308  |
| Quantile regression (0.5 quantile) | 0.1237              | 0.7453              | 0.7473               | 0.994   |
| Quantile regression (0.4 quantile) | 0.1272              | 0.7453              | 0.7475               | 0.9973  |
| Regression tree               | 0.1283              | 0.7212              | 0.7305               | 0.0003259 |
Supplementary Table 7: Performance of the different regression models for the U0126-Wortmannin drug combination. The p-values of two sample t-test comparing the performance of each model with multivariable linear regression (2 explanatory variables) are also reported.

| Model                                                                 | Mean Absolute Error | Pearson correlation | Spearman correlation | P-value       |
|-----------------------------------------------------------------------|---------------------|---------------------|----------------------|---------------|
| Linear regression (2 explanatory variables)                           | 0.1152              | 0.7480              | 0.7182               | -             |
| Linear regression (1 explanatory variables)                           | 0.1208              | 0.7152              | 0.6840               | 1.018e-12     |
| Linear regression (2 explanatory variables plus interaction term)     | 0.1152              | 0.7476              | 0.7182               | 0.9484        |
| Quantile regression (0.5 quantile)                                   | 0.1152              | 0.7480              | 0.7182               | 0.9988        |
| Quantile regression (0.3 quantile)                                   | 0.1289              | 0.7480              | 0.7182               | 0.9933        |
| Regression tree                                                      | 0.1205              | 0.7167              | 0.6964               | 9.93e-05      |
**Supplementary Table 8**: For every combinatorial treatment in enhancers, we report the permuted drug profile, the coefficient of this profile in the linear prediction function, the p-value of one sample t-test comparing the Pearson correlation of the regression model with the Pearson coefficients obtained after permutations of drug profile (assuming approximately Gaussian distributions, null hypothesis: mean of correlation coefficients of the permuted profile is equal to the correlation of the regression model, confidence level: 95%), and the number of the standard deviations which the correlation of the regression model based on the non-permuted drug expression is higher than the mean of correlation coefficients obtained using the permuted drug profile.

|                         | Permuted drug | Coefficient | p-value     | No.of.sd | Permuted drug | Coefficient | p-value     | No.of.sd |
|-------------------------|---------------|-------------|-------------|----------|---------------|-------------|-------------|----------|
| Gefitinib-U0126         | Gefitinib     | 0.262787    | <2.2e-16    | 36.55    | U0126         | 0.642445    | <2.2e-16    | 138.91   |
| Gefitinib-Wortmannin    | Gefitinib     | 0.297348    | <2.2e-16    | 57.47    | Wortmannin    | 0.420427    | <2.2e-16    | 86.37    |
| U0126-Wortmannin        | U0126         | 0.443403    | <2.2e-16    | 100.67   | Wortmannin    | 0.29523     | <2.2e-16    | 47.91    |
**Supplementary Table 9:** Enhancer and promoter pairs which are located within 500 kb of each other and have Pearson correlation (log2cpm values) greater than 0.5 across the samples of our study (21 different samples). These eleven pairs also have Pearson correlation greater than 0.5 across all the FANTOM5 phase 1 samples.

| Enhancer | Promoter | Correlation in our samples | Correlation in f5 samples |
|----------|----------|----------------------------|---------------------------|
| chr1:151485676-151485841 | p1@CGN | 0.530208 | 0.590527 |
| chr10:98032542-98032692 | p1@BLNK | 0.701042 | 0.598473 |
| chr11:85463912-85464270 | p1@SYTL2 | 0.593274 | 0.516982 |
| chr12:69036661-69037118 | p1@ENST00000414313 | 0.903059 | 0.849396 |
| chr12:7592182-7592797 | p1@ENST00000538078 | 0.790416 | 0.948344 |
| chr14:61969529-61970113 | p1@PRKCH | 0.595925 | 0.71889 |
| chr19:13262107-13262928 | p1@S69623 | 0.665645 | 0.622801 |
| chr20:5589880-5590681 | p1@GPCPD1 | 0.596857 | 0.627143 |
| chr5:172192263-172193766 | p1@DUSP1 | 0.572354 | 0.773816 |
| chr8:126525260-126525748 | p1@TRIB1 | 0.514582 | 0.677793 |
| chr9:68455261-68455556 | p2@ENST00000376334 | 0.852421 | 0.789771 |
**Supplementary Table 10:** Enriched GO BP terms in non-linearly described promoters for Gefitinib-U0126 combinatorial treatment.

| GO.ID     | Term                                                   | Annotated | Significant | Expected | P-value   |
|-----------|---------------------------------------------------------|-----------|-------------|----------|-----------|
| GO:0048518 | positive regulation of biological process...            | 2968      | 230         | 180.34   | 3.00E-06  |
| GO:0050794 | regulation of cellular process                          | 5415      | 378         | 329.03   | 5.40E-06  |
| GO:0043627 | response to estrogen                                    | 99        | 19          | 6.02     | 6.30E-06  |
| GO:0050789 | regulation of biological process                        | 5705      | 392         | 346.65   | 1.70E-05  |
| GO:0022414 | reproductive process                                    | 555       | 58          | 33.72    | 2.80E-05  |
| GO:0065007 | biological regulation                                  | 5956      | 404         | 361.91   | 4.40E-05  |
| GO:0032501 | multicellular organismal process                        | 3091      | 231         | 187.82   | 4.70E-05  |
| GO:0097305 | response to alcohol                                    | 164       | 24          | 9.97     | 5.00E-05  |
| GO:0048522 | positive regulation of cellular process                | 2584      | 198         | 157.01   | 5.50E-05  |
| GO:0048545 | response to steroid hormone                            | 197       | 27          | 11.97    | 5.60E-05  |
| GO:0071495 | cellular response to endogenous stimulus               | 602       | 60          | 36.58    | 8.00E-05  |
| GO:0044707 | single-multicellular organism process                  | 2990      | 223         | 181.68   | 8.40E-05  |
| GO:0009719 | response to endogenous stimulus                        | 803       | 75          | 48.79    | 8.80E-05  |
| GO:0030509 | BMP signaling pathway                                 | 56        | 12          | 3.4      | 0.00011   |
| GO:0048731 | system development                                     | 2107      | 165         | 128.03   | 0.00011   |
| GO:0009725 | response to hormone                                   | 482       | 50          | 29.29    | 0.00012   |
| GO:0007165 | signal transduction                                   | 2712      | 204         | 164.79   | 0.00013   |
| GO:0048513 | organ development                                      | 1491      | 123         | 90.6     | 0.00013   |
| GO:0032355 | response to estradiol                                 | 66        | 13          | 4.01     | 0.00014   |
| GO:0007275 | multicellular organismal development                  | 2393      | 183         | 145.41   | 0.00015   |
| GO:0071772 | response to BMP                                       | 58        | 12          | 3.52     | 0.00015   |
| GO:0071773 | cellular response to BMP stimulus                      | 58        | 12          | 3.52     | 0.00015   |
| GO:0014070 | response to organic cyclic compound                    | 386       | 42          | 23.45    | 0.00015   |
| GO:0044700 | single organism signaling                             | 2901      | 215         | 176.27   | 0.00019   |
| GO:0023052 | signaling                                             | 2907      | 215         | 176.64   | 0.00022   |
| GO:2000026 | regulation of multicellular organismal d...            | 752       | 69          | 45.69    | 0.00029   |
| GO:0007154 | cell communication                                     | 3037      | 222         | 184.54   | 0.00034   |
| GO:0009966 | regulation of signal transduction                     | 1422      | 116         | 86.41    | 0.00034   |
| GO:0009888 | tissue development                                     | 894       | 79          | 54.32    | 0.00034   |
| GO:0030198 | extracellular matrix organization                      | 153       | 21          | 9.3      | 0.00036   |
| GO:0051171 | regulation of nitrogen compound metabolism...          | 2680      | 199         | 162.85   | 0.00036   |
| GO:0051239 | regulation of multicellular organismial p...           | 1164      | 98          | 70.73    | 0.00036   |
| GO:0044767 | single-organism developmental process                 | 2854      | 210         | 173.42   | 0.00038   |
| GO:0033993 | response to lipid                                     | 378       | 40          | 22.97    | 0.00039   |
| GO:0043062 | extracellular structure organization                  | 154       | 21          | 9.36     | 0.00039   |
| GO:0009891 | positive regulation of biosynthetic proc...            | 1039      | 89          | 63.13    | 0.0004    |
| GO:0044702 | single organism reproductive process                  | 507       | 50          | 30.81    | 0.00041   |
| GO:0071407 | cellular response to organic cyclic comp...            | 188       | 24          | 11.42    | 0.00042   |
**Supplementary Table 11:** Enriched GO MF terms in non-linearly described promoters for Gefitinib-U0126 combinatorial treatment.

GO.ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the background dataset. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO.ID     | Term                                                                 | Annotated | Significant | Expected | P-value   |
|-----------|----------------------------------------------------------------------|-----------|-------------|----------|-----------|
| GO:0001228| RNA polymerase II transcription regulatory...                         | 156       | 26          | 9.43     | 2.00E-06 |
| GO:0005102| receptor binding                                                      | 609       | 64          | 36.81    | 7.40E-06 |
| GO:0005200| structural constituent of cytoskeleton                               | 48        | 12          | 2.9      | 2.00E-05 |
| GO:0001077| RNA polymerase II core promoter proximal...                          | 114       | 19          | 6.89     | 4.70E-05 |
| GO:0004879| ligand-activated sequence-specific DNA binding...                     | 28        | 8           | 1.69     | 0.00018  |
| GO:0098531| direct ligand regulated sequence-specific...                          | 28        | 8           | 1.69     | 0.00018  |
| GO:0043565| sequence-specific DNA binding                                        | 518       | 52          | 31.31    | 0.00018  |
| GO:0001012| RNA polymerase II regulatory region DNA ...                           | 331       | 37          | 20       | 0.0002   |
| GO:0001071| nucleic acid binding transcription factor...                          | 657       | 62          | 39.71    | 0.00025  |
| GO:0003700| sequence-specific DNA binding transcript...                           | 657       | 62          | 39.71    | 0.00025  |
| GO:0000977| RNA polymerase II regulatory region sequence...                       | 329       | 36          | 19.88    | 0.00037  |
| GO:0046875| ephrin receptor binding                                              | 18        | 6           | 1.09     | 0.00047  |
| GO:0000976| transcription regulatory region sequence...                           | 372       | 39          | 22.48    | 0.0005   |
| GO:0000982| RNA polymerase II core promoter proximal...                          | 170       | 22          | 10.27    | 0.00056  |
| GO:0000978| RNA polymerase II core promoter proximal...                          | 194       | 24          | 11.72    | 0.00063  |
| GO:0000987| core promoter proximal region sequence-s...                           | 201       | 24          | 12.15    | 0.00104  |
| GO:0001159| core promoter proximal region DNA binding...                         | 201       | 24          | 12.15    | 0.00104  |
**Supplementary Table 12:** Enriched GO CC terms in non-linearly described promoters for Gefitinib-U0126 combinatorial treatment.  
GO.ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the background dataset. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO.ID     | Term                        | Annotated | Significant | Expected | P-value   |
|-----------|-----------------------------|-----------|-------------|----------|-----------|
| GO:0071944| cell periphery              | 1869      | 155         | 112.98   | 7.10E-06  |
| GO:0005886| plasma membrane             | 1815      | 150         | 109.72   | 1.30E-05  |
| GO:0031012| extracellular matrix        | 110       | 18          | 6.65     | 9.60E-05  |
| GO:0045111| intermediate filament cytoskeleton | 81       | 14          | 4.9      | 0.00031   |
**Supplementary Table 13:** Enriched GO BP terms in non-linearly described promoters for Gefitinib-Wortmannin combinatorial treatment. GO:ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the non-linearly described promoter set. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO:ID   | Term                              | Annotated | Significant | Expected | P-value |
|---------|-----------------------------------|-----------|-------------|----------|---------|
| GO:0048731 | system development                 | 2107      | 162         | 102.93   | 6.10E-11 |
| GO:0048513 | organ development                  | 1491      | 122         | 72.84    | 1.10E-09 |
| GO:0007275 | multicellular organismal           | 2393      | 173         | 116.91   | 1.60E-09 |
| GO:0044707 | Single multicellular org...        | 2990      | 203         | 146.07   | 5.60E-09 |
| GO:0048856 | anatomical structure d...          | 2546      | 178         | 124.38   | 1.20E-08 |
| GO:0008283 | cell proliferation                 | 1007      | 88          | 49.2     | 2.20E-08 |
| GO:0032501 | multicellular organismal           | 3091      | 205         | 151      | 3.60E-08 |
| GO:0044767 | single-organism develop...         | 2854      | 192         | 139.43   | 4.90E-08 |
| GO:0032502 | developmental process              | 2898      | 194         | 141.58   | 5.90E-08 |
| GO:0014070 | response to organic cyclic         | 386       | 44          | 18.86    | 1.00E-07 |
| GO:0042127 | regulation of cell prolif...       | 752       | 68          | 36.74    | 3.50E-07 |
| GO:0009887 | organ morphogenesis                | 439       | 46          | 21.45    | 6.30E-07 |
| GO:0030154 | cell differentiation               | 1832      | 131         | 89.5     | 9.50E-07 |
| GO:0040011 | locomotion                         | 791       | 69          | 38.64    | 1.10E-06 |
| GO:0097305 | response to alcohol                | 164       | 24          | 8.01     | 1.20E-06 |
| GO:0009653 | anatomical structure mo...          | 1354      | 103         | 66.15    | 1.30E-06 |
| GO:0001944 | vasculature development            | 275       | 33          | 13.43    | 1.40E-06 |
| GO:0072358 | cardiovascular system dev          | 450       | 45          | 21.98    | 3.10E-06 |
| GO:0072359 | circulatory system de...            | 450       | 45          | 21.98    | 3.10E-06 |
| GO:0048545 | response to steroid horm            | 197       | 26          | 9.62     | 3.30E-06 |
| GO:0001568 | blood vessel development            | 261       | 31          | 12.75    | 3.70E-06 |
| GO:2000026 | regulation of multicellular        | 752       | 64          | 36.74    | 6.40E-06 |
| GO:0048869 | cellular developmental pr          | 1989      | 136         | 97.17    | 6.70E-06 |
| GO:0007166 | cell surface receptor sign          | 1354      | 100         | 66.15    | 7.60E-06 |
| GO:0006928 | movement of cell or sub            | 887       | 72          | 43.33    | 8.40E-06 |
| GO:0009888 | tissue development                 | 894       | 72          | 43.67    | 1.10E-05 |
| GO:0001501 | skeletal system develop            | 223       | 27          | 10.89    | 1.10E-05 |
| GO:0006935 | chemotaxis                         | 304       | 33          | 14.85    | 1.30E-05 |
| GO:0042330 | taxis                              | 304       | 33          | 14.85    | 1.30E-05 |
| GO:0050896 | response to stimulus               | 4132      | 244         | 201.86   | 2.40E-05 |
| GO:0048514 | blood vessel morphog               | 221       | 26          | 10.8     | 2.70E-05 |
| GO:0008285 | negative regulation of cell        | 344       | 35          | 16.81    | 2.80E-05 |
| GO:0048646 | anatomical structure form          | 583       | 51          | 28.48    | 3.00E-05 |
| GO:0061035 | regulation of cartilage dev        | 27        | 8           | 1.32     | 3.00E-05 |
| GO:0001525 | angiogenesis                       | 184       | 23          | 8.99     | 3.00E-05 |
| GO:0006915 | apoptotic process                  | 1124      | 84          | 54.91    | 3.20E-05 |
| GO:0044700 | single organism signaling          | 2901      | 181         | 141.72   | 3.50E-05 |
| GO:0051216 | cartilage development              | 82        | 14          | 4.01     | 3.70E-05 |
| GO:0033993 | response to lipid                  | 378       | 37          | 18.47    | 3.80E-05 |
| GO ID          | Term                              | Count | P-Value |
|---------------|-----------------------------------|-------|---------|
| GO:0023052    | signaling                         | 2907  | 142.02  |
| GO:0048705    | skeletal system morphogenesis      | 94    | 4.59    |
| GO:0007435    | salivary gland morphogenesis       | 15    | 0.73    |
| GO:0046683    | response to organophosphates       | 54    | 2.64    |
| GO:0012501    | programmed cell death             | 1140  | 55.69   |
| GO:0048519    | negative regulation of biology     | 2581  | 126.09  |
| GO:0043408    | regulation of MAPK cascades        | 329   | 16.07   |
| GO:0051239    | regulation of multicellular process| 1164  | 56.87   |
| GO:0048704    | embryonic skeletal system          | 38    | 1.86    |
| GO:0007154    | cell communication                 | 3037  | 148.37  |
| GO:0014706    | striated muscle tissue development | 158   | 7.72    |
| GO:0061061    | muscle structure development       | 277   | 13.53   |
| GO:0009725    | response to hormone               | 482   | 23.55   |
| GO:0043627    | response to estrogen              | 99    | 4.84    |
| GO:0001775    | cell activation                   | 439   | 21.45   |
| GO:0009891    | positive regulation of biosynthesis| 1039  | 50.76   |
| GO:0061448    | connective tissue development      | 112   | 5.47    |
| GO:0050794    | regulation of cellular processes   | 5415  | 264.54  |
| GO:0048568    | embryonic organ development        | 212   | 10.36   |
| GO:0007431    | salivary gland develop             | 17    | 0.83    |
| GO:0090257    | regulation of muscle system        | 79    | 3.86    |
| GO:0048523    | negative regulation of cell        | 2398  | 117.15  |
| GO:0071407    | cellular response to organ         | 188   | 9.18    |
| GO:0008544    | epidermis development              | 150   | 7.33    |
| GO:0007411    | axon guidance                      | 215   | 10.5    |
| GO:0097485    | neuron projection guidance         | 215   | 10.5    |
| GO:0008219    | cell death                         | 1196  | 58.43   |
| GO:0044763    | single-organism cellular processes | 6518  | 318.42  |
| GO:0042221    | response to chemical               | 1919  | 93.75   |
| GO:0007165    | signal transduction                | 2712  | 132.49  |
| GO:0048706    | embryonic skeletal system          | 53    | 2.59    |
| GO:0009605    | response to external stimulus      | 1152  | 56.28   |
| GO:0008284    | positive regulation of cell        | 381   | 18.61   |
| GO:000165     | MAPK cascade                       | 369   | 18.03   |
| GO:0023014    | signal transduction by protein     | 385   | 18.81   |
| GO:0002040    | sprouting angiogenesis             | 28    | 1.37    |
| GO:0032355    | response to estradiol              | 66    | 3.22    |
| GO:0098609    | cell-cell adhesion                 | 375   | 18.32   |
| GO:0007399 | nervous system develop | 1151  | 81  | 56.23 | 0.00035 |
|-------------|------------------------|-------|-----|-------|---------|
| GO:1901700  | response to oxygen-cont | 742   | 57  | 36.25 | 0.00036 |
| GO:1901342  | regulation of vasculature | 78    | 12  | 3.81  | 0.00037 |
| GO:0051385  | response to mineralocort | 14    | 5   | 0.68  | 0.00038 |
| GO:0050673  | epithelial cell prolifer | 177   | 20  | 8.65  | 0.00039 |
| GO:0098602  | single organism cell adh | 363   | 33  | 17.73 | 0.0004  |
| GO:0016477  | cell migration | 567   | 46  | 27.7  | 0.00043 |
| GO:0043066  | negative regulation of ap | 504   | 42  | 24.62 | 0.00044 |
| GO:0007517  | muscle organ develop | 153   | 18  | 7.47  | 0.00046 |
| GO:0030198  | extracellular matrix organ | 153   | 18  | 7.47  | 0.00046 |
| GO:0060429  | epithelium development | 570   | 46  | 27.85 | 0.00048 |
| GO:0034109  | homotypic cell-cell adh | 235   | 24  | 11.48 | 0.00048 |
| GO:0010557  | positive regulation of mac | 989   | 71  | 48.32 | 0.00049 |
| GO:0010628  | positive regulation of gen | 1024  | 73  | 50.03 | 0.00049 |
| GO:0050793  | regulation of develop | 1059  | 75  | 51.74 | 0.00049 |
| GO:0043062  | extracellular structure org | 154   | 18  | 7.52  | 0.0005  |
| GO:0035272  | exocrine system develop | 22    | 6   | 1.07  | 0.0005  |
| GO:0022612  | gland morphogenesis | 70    | 11  | 3.42  | 0.00053 |
| GO:0050678  | regulation of epithelial | 142   | 17  | 6.94  | 0.00054 |
| GO:0040012  | regulation of locomotion | 356   | 32  | 17.39 | 0.0006  |
| GO:0048468  | cell development | 1031  | 73  | 50.37 | 0.0006  |
| GO:0043401  | steroid hormone mediat | 31    | 7   | 1.51  | 0.0006  |
| GO:0043069  | negative regulation of pro | 512   | 42  | 25.01 | 0.00061 |
| GO:0006937  | regulation of muscle cont | 50    | 9   | 2.44  | 0.00061 |
| GO:0048732  | gland development | 225   | 23  | 10.99 | 0.00062 |
| GO:0048701  | embryonic cranial skelet | 23    | 6   | 1.12  | 0.00065 |
| GO:0051591  | response to cAMP | 41    | 8   | 2     | 0.0007  |
| GO:0045165  | cell fate commitment | 96    | 13  | 4.69  | 0.00075 |
| GO:0043410  | positive regulation of MA | 214   | 22  | 10.45 | 0.00075 |
| GO:0002042  | cell migration involved in | 16    | 5   | 0.78  | 0.00076 |
| GO:0002521  | leukocyte differentiation | 215   | 22  | 10.5  | 0.0008  |
| GO:1903708  | positive regulation of hem | 74    | 11  | 3.62  | 0.00086 |
| GO:0009719  | response to endogenous | 803   | 59  | 39.23 | 0.00087 |
| GO:0048870  | cell motility | 603   | 47  | 29.46 | 0.00089 |
| GO:0051674  | localization of cell | 603   | 47  | 29.46 | 0.00089 |
| GO:0048522  | positive regulation of cel | 2584  | 156 | 126.24 | 0.00096 |
| GO:1903522  | regulation of blood circul | 75    | 11  | 3.66  | 0.00096 |
| GO:0001936  | regulation of endothelial | 43    | 8   | 2.1   | 0.00098 |
| GO:0031348  | negative regulation of def | 64    | 10  | 3.13  | 0.00099 |
| GO:0048608  | reproductive structure | 219   | 22  | 10.7  | 0.00102 |
| GO:0008347  | glial cell migration | 17    | 5   | 0.83  | 0.00103 |
| GO:0035924  | cellular response to vasc | 17    | 5   | 0.83  | 0.00103 |
| GO:0065007  | biological regulation | 5956  | 321 | 290.97 | 0.00105 |
| GO:0051240  | positive regulation of mul | 625   | 48  | 30.53 | 0.00107 |
| GO:0031325 | positive regulation of cell | 1629 | 105 | 79.58 | 0.00108 |
| GO:0006357 | regulation of transcription | 1088 | 75 | 53.15 | 0.00108 |
| GO:0010033 | response to organic subs | 1486 | 97 | 72.6 | 0.00117 |
| GO:0043010 | camera-type eye devel | 139 | 16 | 6.79 | 0.00119 |
| GO:0022008 | neurogenesis | 797 | 58 | 38.94 | 0.00121 |
| GO:0051270 | regulation of cellular com | 356 | 31 | 17.39 | 0.00122 |
| GO:0061458 | reproductive system dev | 222 | 22 | 10.85 | 0.00123 |
| GO:0051173 | positive regulation of nitr | 1058 | 73 | 51.69 | 0.00124 |
| GO:0060548 | negative regulation of cell | 547 | 43 | 26.72 | 0.00124 |
| GO:0048518 | positive regulation of biol | 2968 | 175 | 145 | 0.00125 |
| GO:2000145 | regulation of cell motility | 326 | 29 | 15.93 | 0.00126 |
| GO:0010171 | body morphogenesis | 35 | 7 | 1.71 | 0.00129 |
| GO:0045785 | positive regulation of cell | 167 | 18 | 8.16 | 0.0013 |
| GO:0051716 | cellular response to stim | 3544 | 204 | 173.14 | 0.00131 |
| GO:0002062 | chondrocyte differentiat | 45 | 8 | 2.2 | 0.00133 |
| GO:0045778 | positive regulation of ossi | 45 | 8 | 2.2 | 0.00133 |
| GO:0044057 | regulation of system proc | 154 | 17 | 7.52 | 0.00135 |
| GO:0045595 | regulation of cell differen | 734 | 54 | 35.86 | 0.00141 |
| GO:0007155 | cell adhesion | 617 | 47 | 30.14 | 0.00144 |
| GO:0010562 | positive regulation of pho | 470 | 38 | 22.96 | 0.00144 |
| GO:0045937 | positive regulation of pho | 470 | 38 | 22.96 | 0.00144 |
| GO:1901698 | response to nitrogen com | 470 | 38 | 22.96 | 0.00144 |
| GO:0048562 | embryonic organ morp | 129 | 15 | 6.3 | 0.00152 |
| GO:0022610 | biological adhesion | 619 | 47 | 30.24 | 0.00153 |
| GO:0032846 | positive regulation of ho | 68 | 10 | 3.32 | 0.00159 |
| GO:0050789 | regulation of biological pr | 5705 | 308 | 278.71 | 0.00165 |
| GO:0019220 | regulation of phosphate | 842 | 60 | 41.13 | 0.00166 |
| GO:0001503 | ossification | 185 | 19 | 9.04 | 0.00171 |
**Supplementary Table 14**: Enriched GO MF terms in non-linearly described promoters for Gefitinib-Wortmannin combinatorial treatment. GO.ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the background dataset. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO.ID       | Term                                           | Annotated | Significant | Expected | P-value  |
|-------------|------------------------------------------------|-----------|-------------|----------|----------|
| GO:0008307  | structural constituent of muscle               | 11        | 6           | 0.54     | 4.80E-06 |
| GO:0000981  | sequence-specific DNA binding RNA polyme...    | 314       | 32          | 15.27    | 5.60E-05 |
| GO:0004879  | ligand-activated sequence-specific DNA b...    | 28        | 7           | 1.36     | 0.0003   |
| GO:0098531  | direct ligand regulated sequence-specific      | 28        | 7           | 1.36     | 0.0003   |
| GO:0005102  | receptor binding                               | 609       | 49          | 29.63    | 0.00031  |
**Supplementary Table 15:** Enriched GO BP terms in non-linearly described promoters for U0126-Wortmannin combinatorial treatment.  
**GO.ID:** Gene Ontology ID. **Term:** Description string. **Annotated:** number of genes annotated with this GO id in the background dataset. **Significant:** the actual number of genes annotated with this GO id in the non-linearly described promoter set. **Expected:** the expected number of genes annotated with this GO id in the non-linearly described promoter set. **P-value:** the p-value of the test.

| GO.ID     | Term                                      | Annotated | Significant | Expected | P-value |
|-----------|-------------------------------------------|-----------|-------------|----------|---------|
| GO:0045653| negative regulation of megakaryocyte differ... | 17        | 15          | 0.85     | 2.90E-18|
| GO:1901533| negative regulation of hematopoietic process | 21        | 16          | 1.05     | 1.80E-17|
| GO:0035574| histone H4-K20 demethylation              | 16        | 14          | 0.8      | 5.30E-17|
| GO:1901532| regulation of hematopoietic progenitor c... | 34        | 18          | 1.69     | 2.70E-15|
| GO:0045652| regulation of megakaryocyte differentiation| 22        | 15          | 1.1      | 2.90E-15|
| GO:0030219| megakaryocyte differentiation             | 38        | 16          | 1.89     | 9.00E-12|
| GO:0070076| histone lysine demethylation              | 29        | 14          | 1.45     | 1.90E-11|
| GO:0016577| histone demethylation                     | 31        | 14          | 1.55     | 5.80E-11|
| GO:0051290| protein heterotetramerization             | 31        | 14          | 1.55     | 5.80E-11|
| GO:0006335| DNA replication-dependent nucleosome associ... | 32        | 14          | 1.6      | 9.90E-11|
| GO:0032776| DNA methylation on cytosine               | 32        | 14          | 1.6      | 9.90E-11|
| GO:0034723| DNA replication-dependent nucleosome org... | 32        | 14          | 1.6      | 9.90E-11|
| GO:0006482| protein demethylation                     | 33        | 14          | 1.64     | 1.60E-10|
| GO:0008214| protein dealkylation                      | 33        | 14          | 1.64     | 1.60E-10|
| GO:0000183| chromatin silencing at rDNA                | 39        | 15          | 1.94     | 1.90E-10|
| GO:0070988| demethylation                             | 44        | 15          | 2.19     | 1.40E-09|
| GO:0045638| negative regulation of myeloid cell differ... | 53        | 16          | 2.64     | 3.00E-09|
| GO:0034080| CENP-A containing nucleosome assembly      | 42        | 14          | 2.09     | 7.00E-09|
| GO:0061641| CENP-A containing chromatin organization   | 42        | 14          | 2.09     | 7.00E-09|
| GO:1903707| negative regulation of hemopoiesis        | 72        | 18          | 3.59     | 8.80E-09|
| GO:0031055| chromatin remodeling at centromere        | 43        | 14          | 2.14     | 9.90E-09|
| GO:0002244| hematopoietic progenitor cell differentiation | 107       | 22          | 5.33     | 1.00E-08|
| GO:0034508| centromere complex assembly               | 50        | 15          | 2.49     | 1.00E-08|
| GO:0006305| DNA alkylation                            | 67        | 17          | 3.34     | 1.80E-08|
| GO:0006306| DNA methylation                           | 67        | 17          | 3.34     | 1.80E-08|
| GO:1903706| regulation of hemopoiesis                 | 164       | 27          | 8.17     | 3.30E-08|
| GO:0043486| histone exchange                          | 47        | 14          | 2.34     | 3.60E-08|
| GO:0044728| DNA methylation or demethylation          | 74        | 17          | 3.69     | 8.80E-08|
| GO:0043044| ATP-dependent chromatin remodeling        | 66        | 16          | 3.29     | 9.50E-08|
| GO:0006352| DNA-templated transcription, initiation    | 259       | 34          | 12.91    | 1.80E-07|
| GO:0006336| DNA replication-independent nucleosome ass... | 53        | 14          | 2.64     | 1.90E-07|
| GO:0034724| DNA replication-independent nucleosome org... | 53        | 14          | 2.64     | 1.90E-07|
| GO:0030154| cell differentiation                      | 1832      | 135         | 91.32    | 3.50E-07|
| GO:0006304| DNA modification                          | 90        | 18          | 4.49     | 3.50E-07|
| GO:0016458| gene silencing                            | 121       | 21          | 6.03     | 4.60E-07|
| GO:0006342| chromatin silencing                       | 65        | 15          | 3.24     | 4.80E-07|
| GO:0006338| chromatin remodeling                      | 133       | 22          | 6.63     | 5.80E-07|
| GO:0051291| protein heterooligomerization             | 77        | 16          | 3.84     | 9.10E-07|
| GO:0051262| protein tetramerization                   | 96        | 18          | 4.79     | 9.50E-07|
| GO:0045637| regulation of myeloid cell differentiation | 109       | 19          | 5.43     | 1.50E-06|
| GO:0032502       | developmental process              | 2898 | 190 | 144.45 | 2.50E-06 |
|------------------|-----------------------------------|------|-----|--------|-----------|
| GO:0044767       | single-organism developmental process | 2854 | 186 | 142.26 | 5.40E-06 |
| GO:0007275       | multicellular organismal development | 2393 | 161 | 119.28 | 5.70E-06 |
| GO:0048513       | organ development                  | 1491 | 109 | 74.32  | 1.10E-05 |
| GO:2000026       | regulation of multicellular organismal development | 752  | 64  | 37.48  | 1.20E-05 |
| GO:0048869       | cellular developmental process     | 1989 | 137 | 99.14  | 1.30E-05 |
| GO:0044707       | single-multicellular organism process | 2990 | 191 | 149.04 | 1.40E-05 |
| GO:0001944       | vasculature development            | 275  | 31  | 13.71  | 1.60E-05 |
| GO:0065004       | protein-DNA complex assembly       | 151  | 21  | 7.53   | 1.80E-05 |
| GO:0002683       | negative regulation of immune system process | 175  | 23  | 8.72   | 1.80E-05 |
| GO:0045596       | negative regulation of cell differentiation | 925  | 73  | 46.11  | 3.90E-05 |
| GO:0032501       | multicellular organismal process   | 3091 | 195 | 154.07 | 2.50E-05 |
| GO:1901342       | regulation of vasculature development | 78   | 14  | 3.89   | 2.60E-05 |
| GO:0000723       | telomere maintenance               | 80   | 14  | 3.99   | 3.50E-05 |
| GO:0043414       | macromolecule methylation          | 209  | 24  | 10.42  | 0.00011  |
| GO:0048534       | hematopoietic or lymphoid organ development | 420  | 39  | 20.94  | 0.00012  |
| GO:0071824       | protein-DNA complex subunit organization | 172  | 21  | 8.57   | 0.00012  |
| GO:0045595       | regulation of cell differentiation  | 734  | 59  | 36.59  | 0.00014  |
| GO:0032200       | telomere organization              | 82   | 14  | 4.09   | 4.60E-05 |
| GO:0051172       | negative regulation of nitrogen compound... | 967  | 75  | 48.2   | 5.40E-05 |
| GO:0009890       | negative regulation of biosynthetic process... | 937  | 73  | 46.71  | 5.90E-05 |
| GO:0010558       | negative regulation of macromolecule bio... | 905  | 71  | 45.11  | 6.10E-05 |
| GO:0048856       | anatomical structure development    | 2546 | 164 | 126.91 | 6.10E-05 |
| GO:0050793       | regulation of developmental process | 1059 | 80  | 52.79  | 7.20E-05 |
| GO:0048731       | system development                 | 2107 | 139 | 105.02 | 0.0001  |
| GO:0043414       | macromolecule methylation          | 209  | 24  | 10.42  | 0.00011  |
| GO:0048534       | hematopoietic or lymphoid organ development | 420  | 39  | 20.94  | 0.00012  |
| GO:0071824       | protein-DNA complex subunit organization | 172  | 21  | 8.57   | 0.00012  |
| GO:0051259       | protein oligomerization             | 281  | 28  | 14.01  | 0.00035  |
| GO:0001763       | morphogenesis of a branching structure | 99   | 14  | 4.93   | 0.00037  |
| GO:0045746       | negative regulation of Notch signaling process... | 14   | 5   | 0.7    | 0.00041  |
| GO:0006334       | nucleosome assembly                 | 112  | 15  | 5.58   | 0.00042  |
| GO:0045814       | negative regulation of gene expression, process... | 112  | 15  | 5.58   | 0.00042  |
| GO          | Term                                    | Count | Diff | FDR   |
|-------------|-----------------------------------------|-------|------|-------|
| GO:0031497  | chromatin assembly                      | 125   | 6.23 | 0.00046 |
| GO:0097191  | extrinsic apoptotic signaling pathway    | 150   | 7.48 | 0.00046 |
| GO:0045765  | regulation of angiogenesis              | 70    | 3.49 | 0.00063 |
| GO:0051093  | negative regulation of developmental pro... | 388  | 19.34 | 0.00092 |
| GO:0060249  | anatomical structure homeostasis        | 173   | 8.62 | 0.00098 |
| GO:0045934  | negative regulation of nucleobase-contai... | 892  | 44.46 | 0.001 |
Supplementary Table 16: Enriched GO MF terms in non-linearly described promoters for U0126-Wortmannin combinatorial treatment. GO.ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the background dataset. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO.ID     | Term                                          | Annotated | Significant | Expected | P-value   |
|-----------|-----------------------------------------------|-----------|-------------|----------|-----------|
| GO:0035575| histone demethylase activity (H4-K20 spe...)  | 16        | 14          | 0.78     | 3.90E-17  |
| GO:0032452| histone demethylase activity                  | 29        | 14          | 1.41     | 1.40E-11  |
| GO:0032451| demethylase activity                          | 35        | 15          | 1.71     | 2.20E-11  |
| GO:0042393| histone binding                               | 142       | 20          | 6.92     | 1.70E-05  |
| GO:0000981| RNA polymerase II transcription factor a...    | 314       | 32          | 15.31    | 5.80E-05  |
| GO:0043565| sequence-specific DNA binding                 | 518       | 44          | 25.25    | 0.0002    |
| GO:0044212| transcription regulatory region DNA bind...    | 465       | 40          | 22.67    | 0.00031   |
| GO:0000975| regulatory region DNA binding                 | 467       | 40          | 22.77    | 0.00034   |
| GO:0001067| regulatory region nucleic acid binding        | 467       | 40          | 22.77    | 0.00034   |
| GO:0003677| DNA binding                                   | 1562      | 103         | 76.15    | 0.00053   |
| GO:0001071| nucleic acid binding transcription facto...    | 657       | 51          | 32.03    | 0.00057   |
| GO:0003700| transcription factor activity, sequence-...    | 657       | 51          | 32.03    | 0.00057   |
| GO:0000977| RNA polymerase II regulatory region sequ...    | 329       | 30          | 16.04    | 0.00068   |
| GO:0001012| RNA polymerase II regulatory region DNA ...    | 331       | 30          | 16.14    | 0.00075   |
**Supplementary Table 17**: Enriched GO CC terms in non-linearly described promoters for U0126-Wortmannin combinatorial treatment. GO.ID: Gene Ontology ID. Term: Description string. Annotated: number of genes annotated with this GO id in the background dataset. Significant: the actual number of genes annotated with this GO id in the non-linearly described promoter set. Expected: the expected number of genes annotated with this GO id in the non-linearly described promoter set. P-value: the p-value of the test.

| GO.ID   | Term                       | Annotated | Significant | Expected | P-value  |
|---------|----------------------------|-----------|-------------|----------|----------|
| GO:0000786 | nucleosome                 | 77        | 14          | 3.79     | 2.00E-05 |
| GO:0044815 | DNA packaging complex     | 83        | 14          | 4.09     | 4.70E-05 |
**Supplementary Table 18:** Overrepresented motifs in non-linearly described promoters for Gefitinib-U0126 combinatorial treatment. In the first column the names of the overrepresented motifs are listed. The p-value after BH adjustment is reported. The observed ratio denotes the number of occurrences of the motif in the non-linearly described promoters divided by number of the non-linearly described promoters. The background ratio denotes the number of occurrences of the motif in the under study promoters divided by the number of the under study promoters. Odds ratio is the observed ratio divided by the background ratio.

|        | p-value | obs_ratio | back_ratio | odds_ratio |
|--------|---------|-----------|------------|------------|
| PITX1..3 | 0.001029 | 36/1001   | 313/19414  | 2.230689   |
| FOXP1   | 1.41E−09 | 113/1001  | 1105/19414 | 1.98334    |
| ZBTB16  | 0.001029 | 27/1001   | 206/19414  | 2.542011   |
| HMGA1,2 | 0.029173 | 18/1001   | 150/19414  | 2.327353   |
| NKX6-1,2| 0.007534 | 19/1001   | 141/19414  | 2.613457   |
| EVII    | 0.006915 | 21/1001   | 161/19414  | 2.529731   |
| PRRX1,2 | 0.015723 | 18/1001   | 140/19414  | 2.493592   |
**Supplementary Table 19**: Overrepresented motifs in non-linearly described for Gefitinib-Wortmannin combinatorial treatment. In the first column the names of the overrepresented motifs are listed. The p-value after BH adjustment is reported. The observed ratio denotes the number of occurrences of the motif in the non-linearly described promoters divided by number of the non-linearly described promoters. The background ratio denotes the number of occurrences of the motif in the under study promoters divided by the number of the under study promoters. Odds ratio is the observed ratio divided by the background ratio.

| Motif         | p-value | obs_ratio | back_ratio | odds_ratio |
|---------------|---------|-----------|------------|------------|
| GATA4         | 0.0234  | 36/953    | 423/19414  | 1.733741   |
| NR1H4         | 0.008592| 20/953    | 170/19414  | 2.396642   |
| TOPORS        | 0.002426| 38/953    | 386/19414  | 2.00548    |
| PAX4          | 0.039172| 15/953    | 136/19414  | 2.246852   |
| TEF           | 0.007379| 12/953    | 72/19414   | 3.395243   |
| FOXL1         | 0.004492| 19/953    | 146/19414  | 2.65108    |
| LHX3,4        | 0.049624| 8/953     | 54/19414   | 3.017994   |
| PITX1,3       | 0.041923| 27/953    | 313/19414  | 1.757282   |
| FOXP1         | 6.76E-10| 110/953   | 1105/19414 | 2.029792   |
| ZBTB16        | 0.001206| 26/953    | 206/19414  | 2.571155   |
| POU1F1        | 0.041923| 9/953     | 63/19414   | 2.910208   |
| STAT2,4,6     | 0.024437| 42/953    | 523/19414  | 1.635949   |
| DBP           | 0.028931| 20/953    | 199/19414  | 2.047383   |
| FOXD3         | 0.044731| 16/953    | 155/19414  | 2.10286    |
| IRF1,2        | 0.024543| 36/953    | 434/19414  | 1.689798   |
| CDX1,2,4      | 0.002056| 23/953    | 179/19414  | 2.617562   |
| HMG1,2        | 0.024437| 17/953    | 150/19414  | 2.308765   |
| NKx6-1,2      | 0.015666| 17/953    | 141/19414  | 2.456133   |
| ONECUT1,2     | 0.002962| 15/953    | 94/19414   | 3.250765   |
| EVI1          | 0.000259| 24/953    | 161/19414  | 3.036739   |
| CRX           | 0.024543| 16/953    | 140/19414  | 2.328167   |
| PRRX1,2       | 0.024543| 16/953    | 140/19414  | 2.328167   |
| HBPl_HMGB_SSRP1_UBTF | 0.041923| 22/953    | 239/19414  | 1.875197   |
**Supplementary Table 20:** Overrepresented motifs in non-linearly described promoters for U0126-Wortmannin combinatorial treatment. In the first column the names of the overrepresented motifs are listed. The p-value after BH adjustment is reported. The observed ratio denotes the number of occurrences of the motif in the non-linearly described promoters divided by number of the non-linearly described promoters. The background ratio denotes the number of occurrences of the motif in the under study promoters divided by the number of the under study promoters. Odds ratio is the observed ratio divided by the background ratio.

| Motif          | p-value     | obs_ratio | back_ratio | odds_ratio |
|----------------|-------------|-----------|------------|------------|
| TOPORS         | 0.003924    | 37/923    | 386/19414  | 2.016173   |
| FOXL1          | 0.010522    | 18/923    | 146/19414  | 2.593182   |
| PITX1..3       | 0.010522    | 30/923    | 313/19414  | 2.015999   |
| FOXP1          | 1.02E-08    | 104/923   | 1105/19414 | 1.979632   |
| ZBTB16         | 0.003924    | 24/923    | 206/19414  | 2.450515   |
| NKX3-1         | 0.018264    | 19/923    | 160/19414  | 2.505598   |
| OCT4_SOX2{dimer} | 0.041242  | 16/923    | 146/19414  | 2.305051   |
| FOXD3          | 0.003924    | 20/923    | 155/19414  | 2.714011   |
| FOXO1,3,4      | 0.018264    | 23/923    | 227/19414  | 2.131156   |
| EVI1           | 0.020158    | 18/923    | 161/19414  | 2.351581   |
Supplementary Table 21: Common motifs overrepresented in not linearly described promoters. For every drug combination the odds ratios and p-values after BH adjustment are reported. Odds ratio is the observed ratio divided by the background ratio. Performing the enrichment analysis excluding the common promoters among the non-linearly described ones for every combinatorial treatment revealed that the common overrepresented motifs are due to the promoter regions shared between the treatments. Specifically, the enrichment analysis after BH adjustment yielded no enriched motifs for the Gefitinib-U0126 pair, two enriched motifs (FOXP1, EVI1) for the Gefitinib Wortmannin pair and two enriched motifs the (FOXP1, FOXD3) for U0126-Wortmannin pair.

| Motifs | Gefitinib_U0126 | Gefitinib_Wortmannin | U0126_Wortmannin |
|--------|-----------------|---------------------|-----------------|
|        | Odds ratio      | P-value             | Odds ratio      | P-value             | Odds ratio | P-value |
| **EVI1** | 2.53           | 6.91e-03            | 3.04           | 2.59e-04            | 2.35      | 2.02e-02 |
| **FOXP1** | 1.98           | 1.41e-09            | 2.03           | 6.76e-10            | 1.98      | 1.02e-08 |
| **PITX1..3** | 2.23          | 1.03e-03            | 1.76           | 4.19e-02            | 2.02      | 1.05e-02 |
| **ZBTB16** | 2.54           | 1.03e-03            | 2.57           | 1.21e-03            | 2.45      | 3.92e-03 |
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