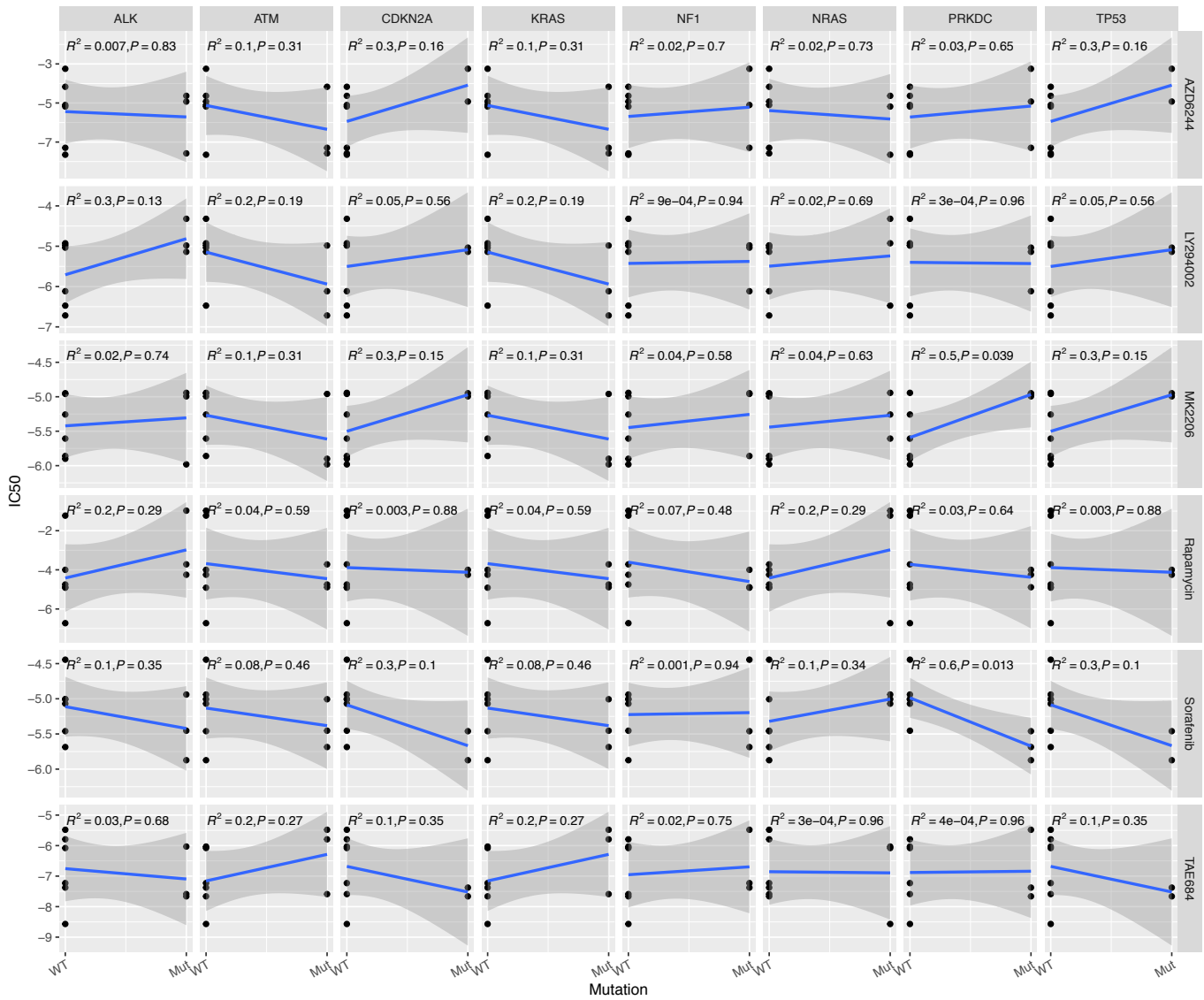
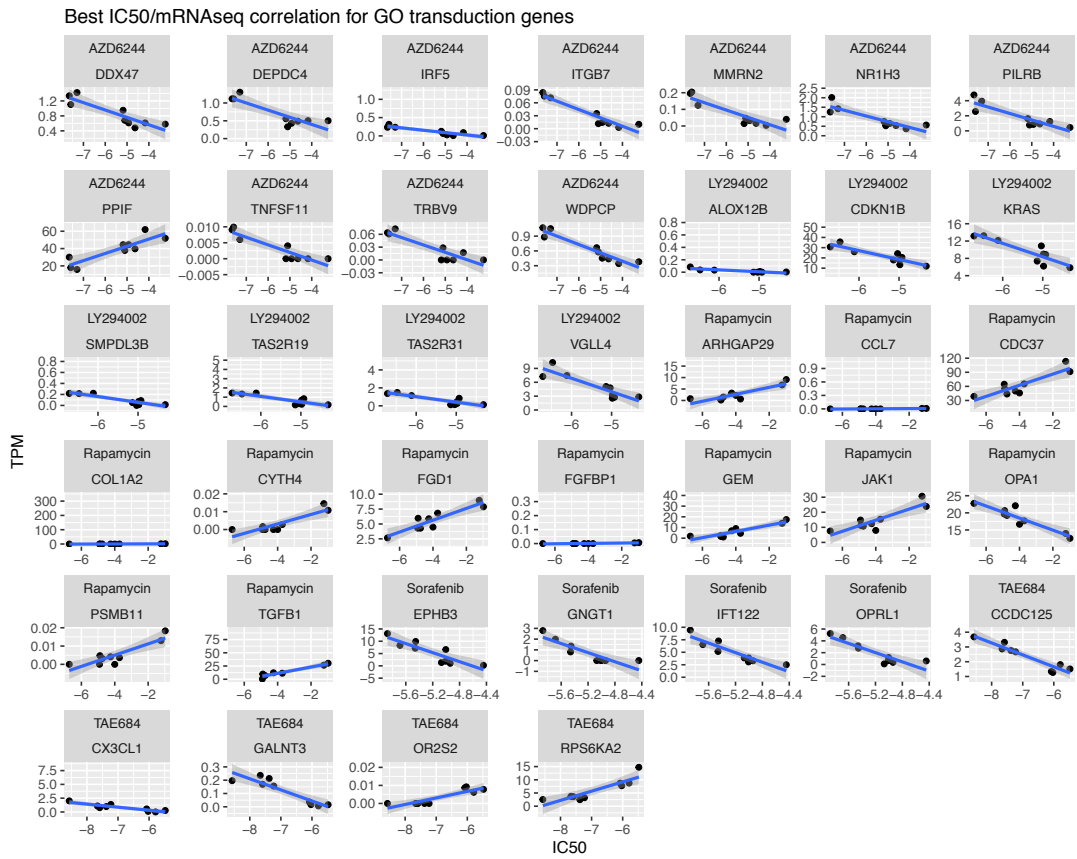
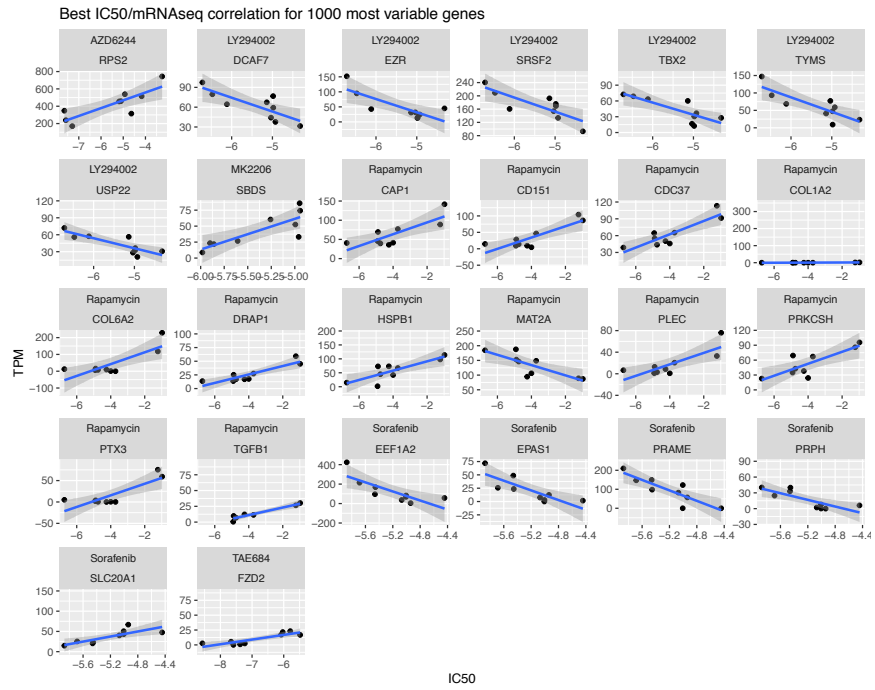


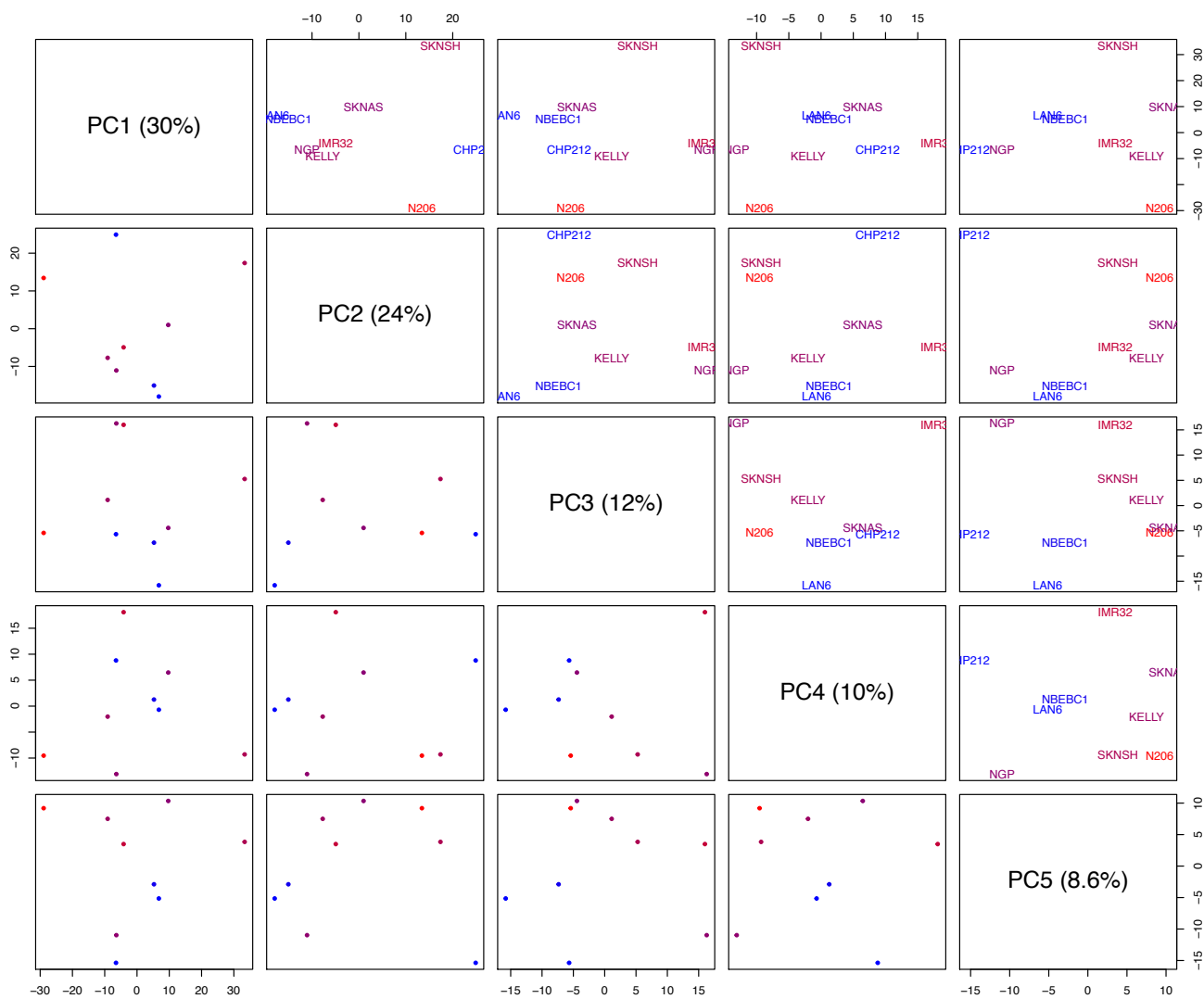
Supplementary Figure 1: Annotated IC<sub>50</sub> of all measured drugs.



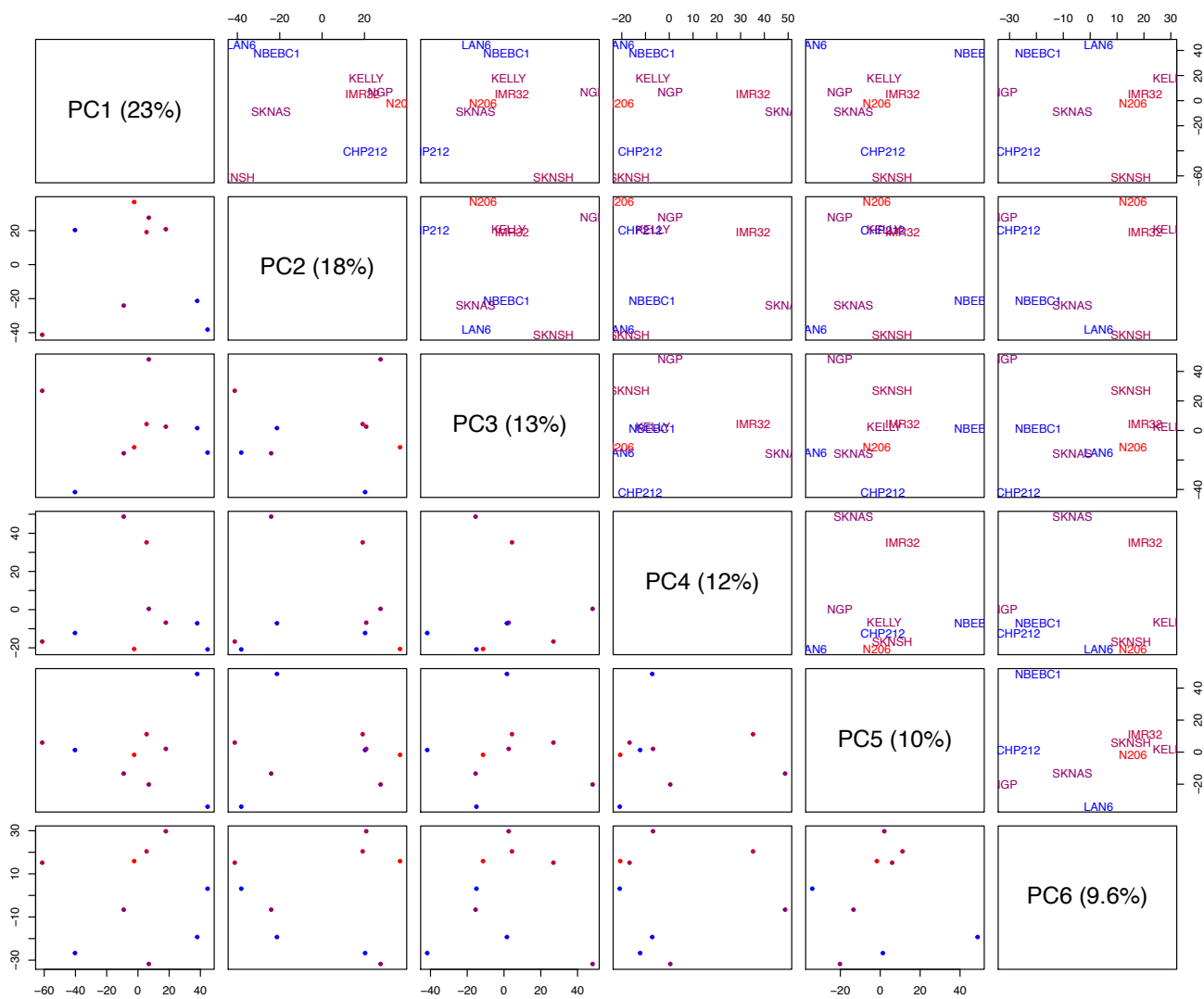
Supplementary Figure 2: (Correlation between IC50 and mutation status for RAS/P53 genes with mutation frequency between 30% and 70% in our panel.



Supplementary Figure 3: Top correlations between IC50 and mRNA expression for the 1000 most variable genes (top, adjusted  $p > 0.95$ ) and GO signal transduction genes (bottom, adjusted  $p > 0.95$ ).

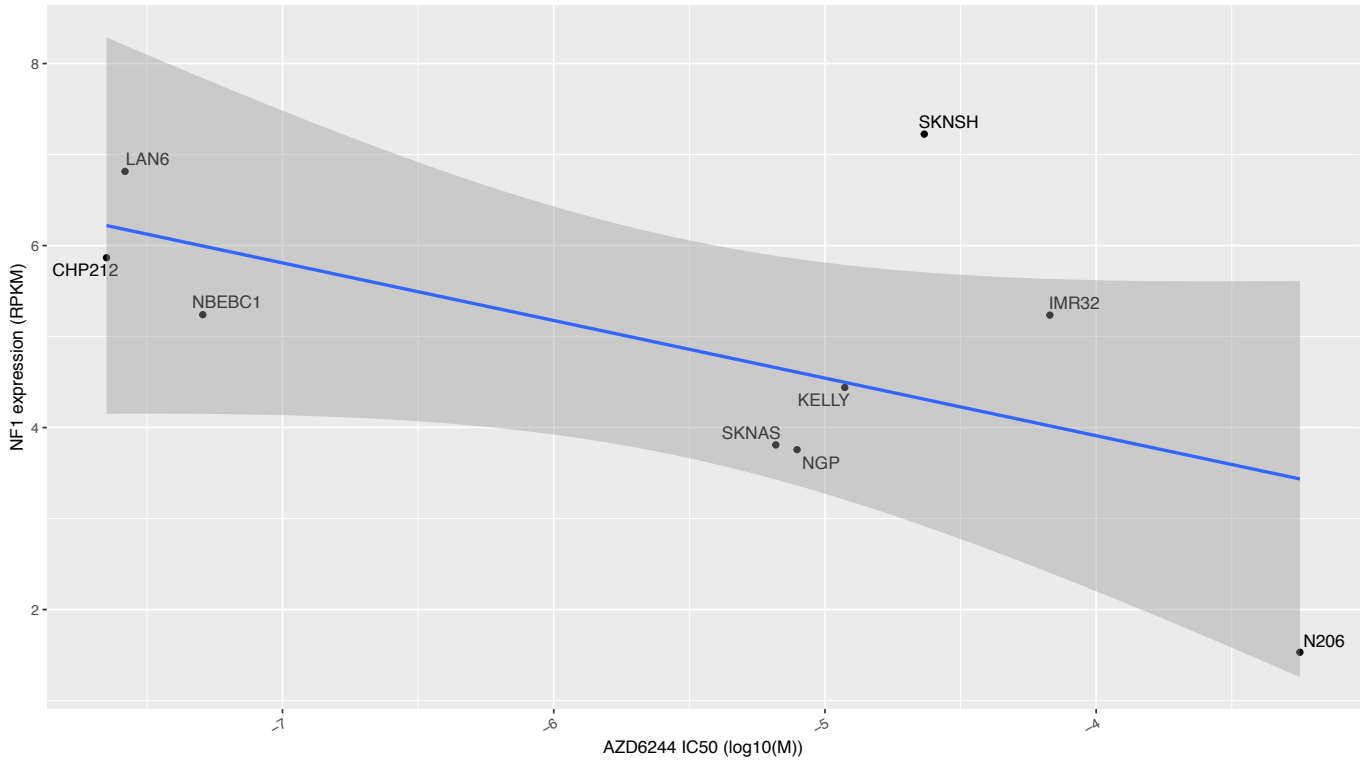


Supplementary Figure 4: Principal Component Analysis of the 1000 most variable genes. All components up to the first one explaining less than 10% of the variance are shown.

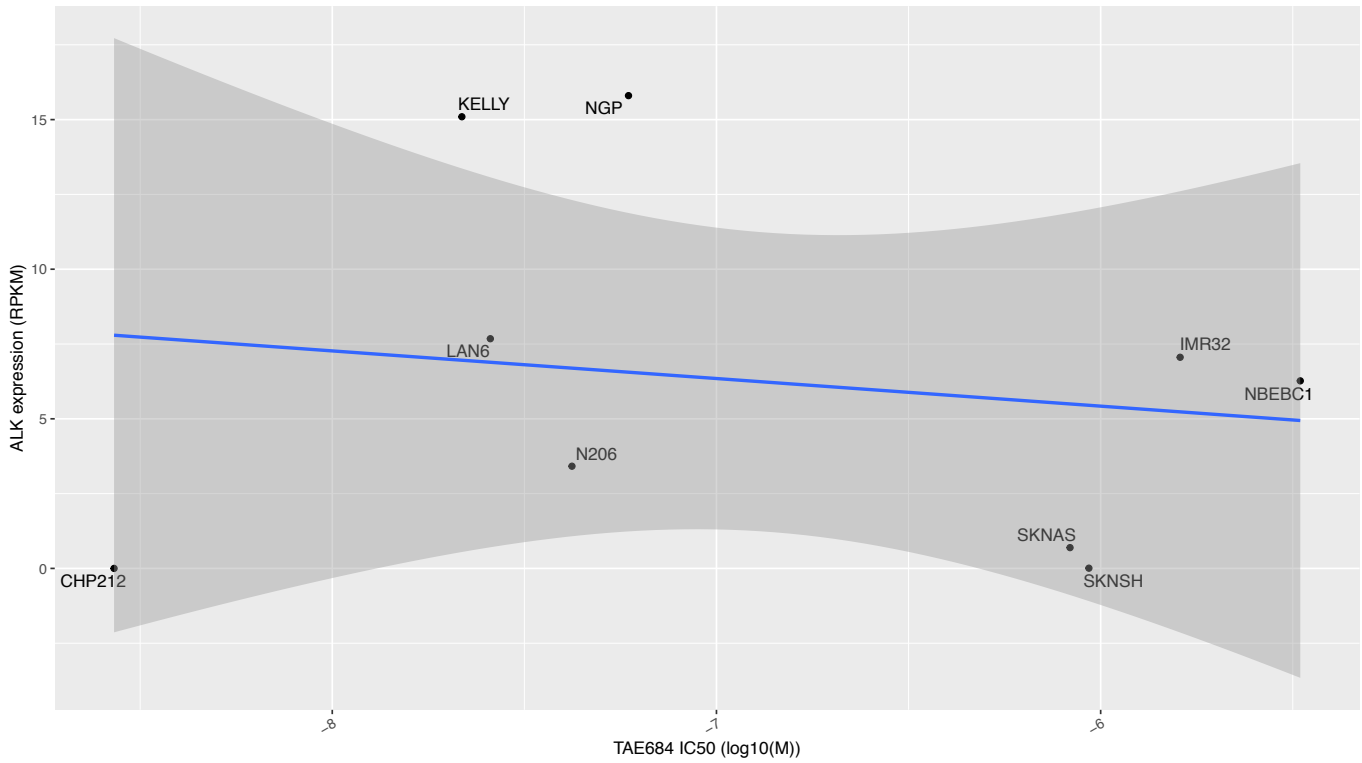


Supplementary Figure 5: Principal Component Analysis of the 5262 signal transduction genes as annotated in the Gene Ontology knowledgebase. All components up to the first one explaining less than 10% of the variance are shown.

AZD6244 IC50 vs NF1 expression, R2= 0.34 p-value= 0.102

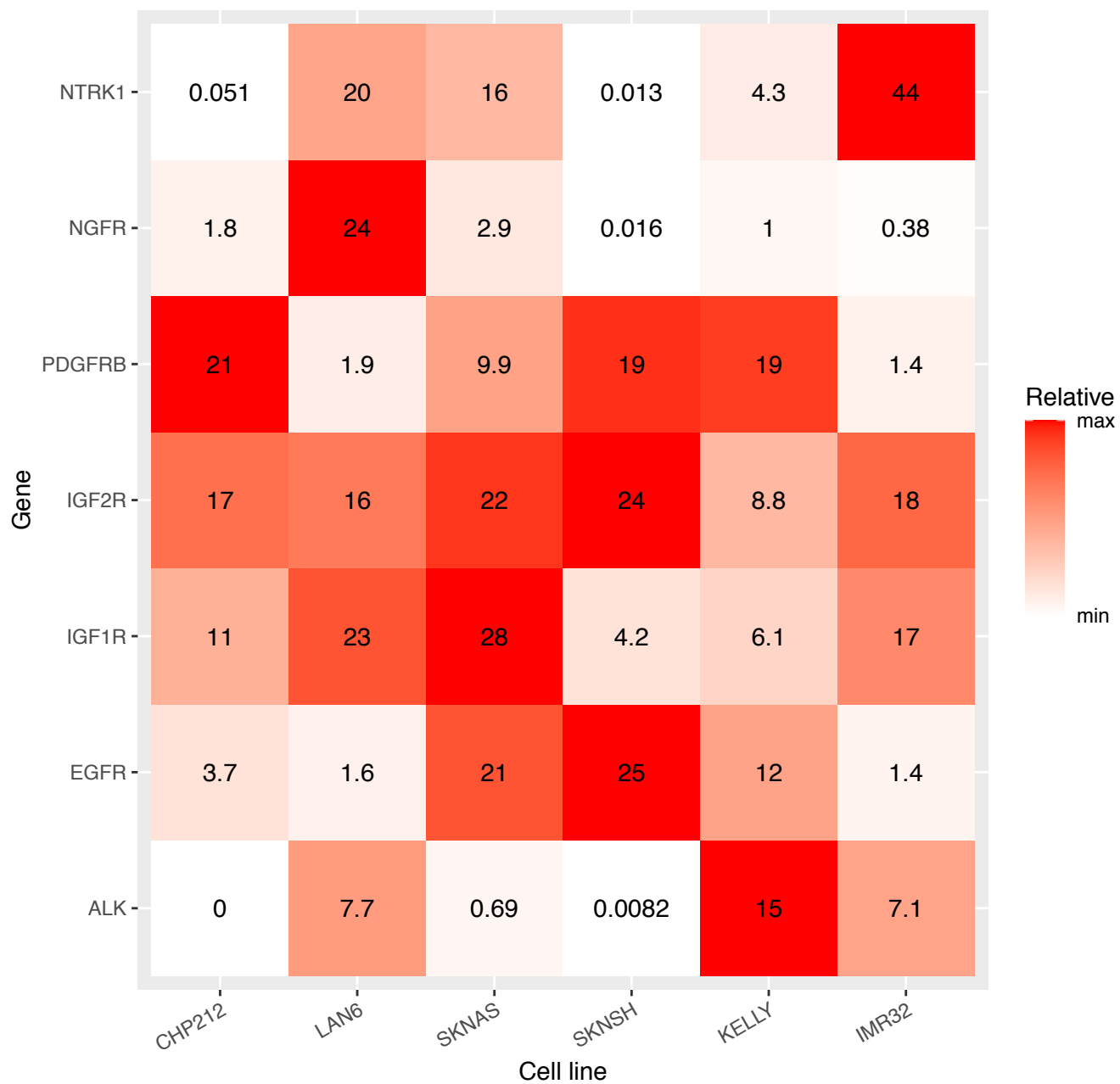


TAE684 IC50 vs ALK expression, R2= 0.0079 p-value= 0.82



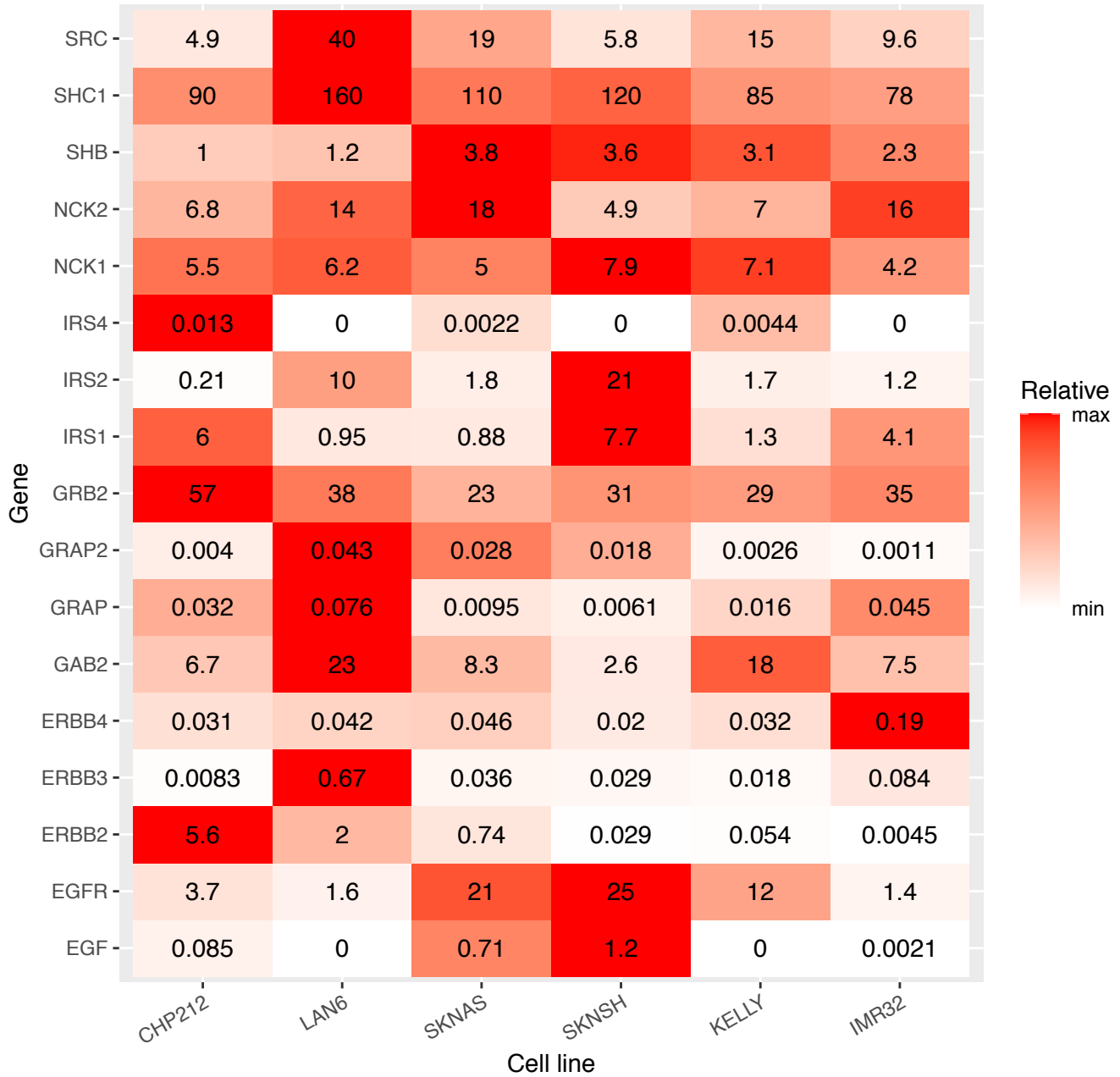
Supplementary Figure 6: NF1 expression versus AZD6244 IC50 and ALK expression versus TAE684 IC50.

### Target receptors expression



Supplementary Figure 7: Receptors RNA expression (TPM).

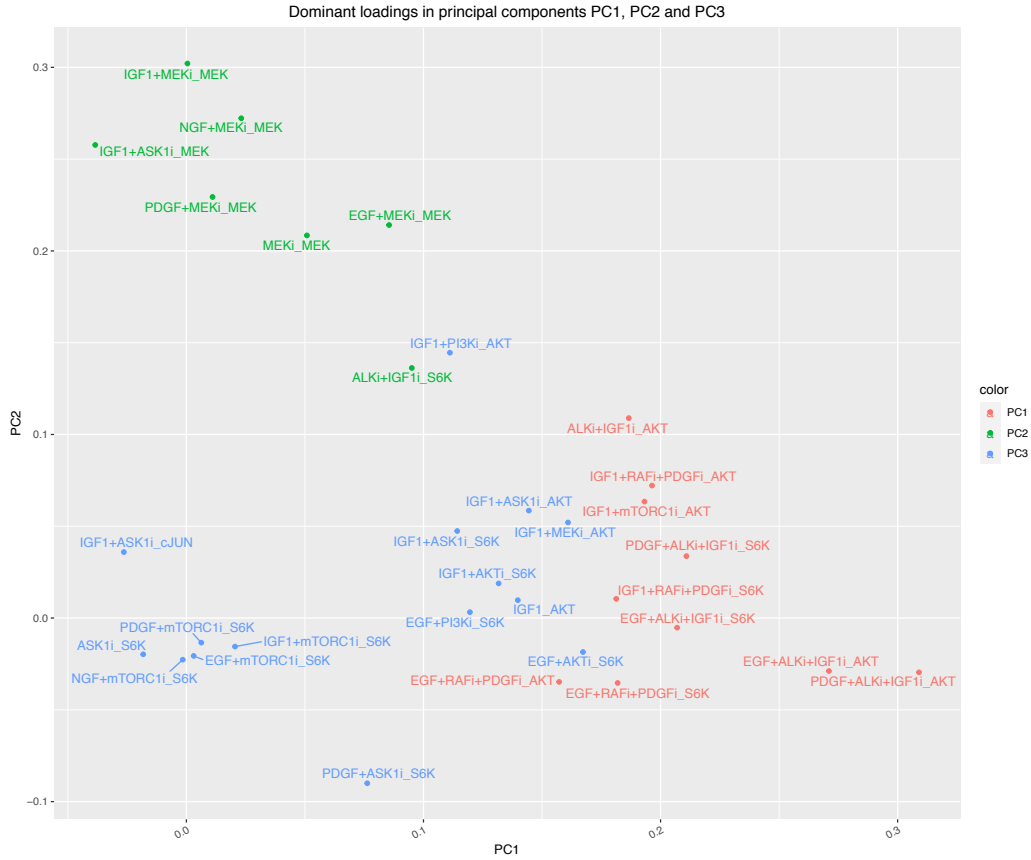
### Adaptor & ERBB family expression



Supplementary Figure 8: Adaptors and ERBB receptor family RNA expression (TPM).



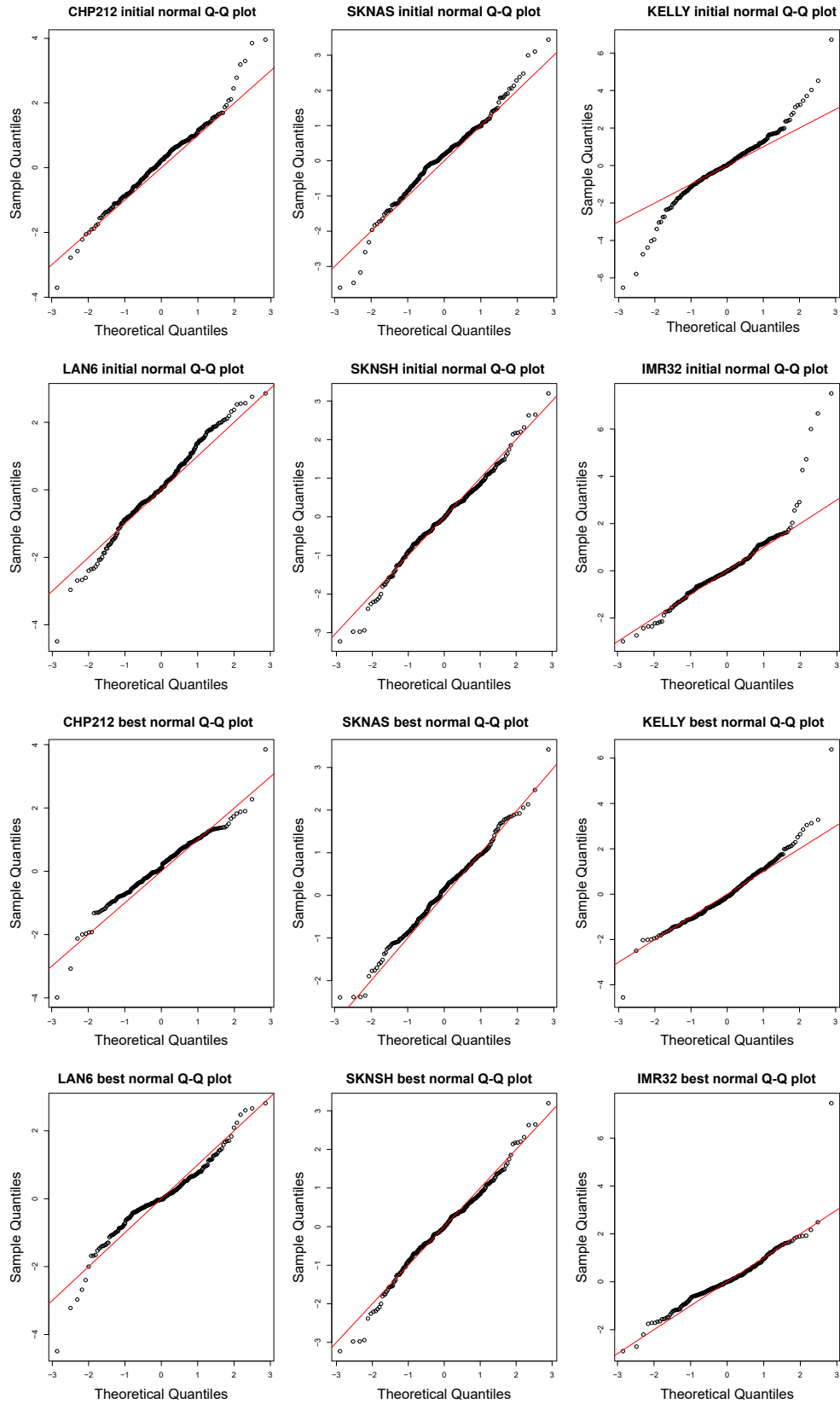




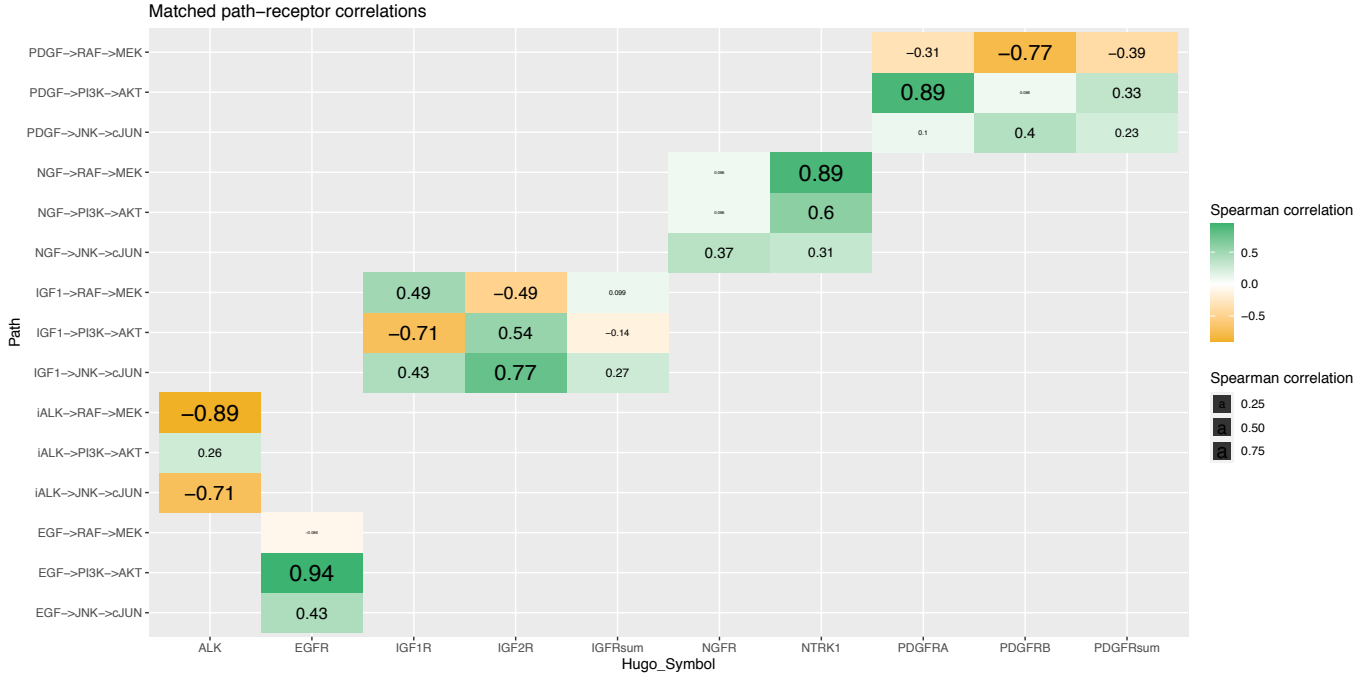
Supplementary Figure 10: Main loadings in the first 3 principal components of the perturbation data PCA. Color corresponds to the components for which the condition has the highest absolute weight.

Condition	PC1	Condition	PC2	Condition	PC3
PDGF+ALKi+IGF1i_AKT	0.309	IGF1+MEKi_MEK	0.302	IGF1+ASK1i_MEK	-0.235
EGF+ALKi+IGF1i_AKT	0.271	NGF+MEKi_MEK	0.272	IGF1+PI3Ki_AKT	-0.213
PDGF+ALKi+IGF1i_S6K	0.211	IGF1+ASK1i_MEK	0.258	IGF1+mTORC1i_S6K	-0.210
EGF+ALKi+IGF1i_S6K	0.207	PDGF+MEKi_MEK	0.229	PDGF+ASK1i_S6K	-0.209
IGF1+RAFi+PDGFi_AKT	0.196	EGF+MEKi_MEK	0.214	PDGF+mTORC1i_S6K	-0.208
IGF1+mTORC1i_AKT	0.193	MEKi_MEK	0.208	NGF+mTORC1i_S6K	-0.202
ALKi+IGF1i_AKT	0.187	IGF1+PI3Ki_AKT	0.145	IGF1_AKT	-0.200
EGF+RAFi+PDGFi_S6K	0.182	ALKi+IGF1i_S6K	0.136	EGF+PI3Ki_S6K	0.183
IGF1+RAFi+PDGFi_S6K	0.181	EGF+ASK1i_AKT	-0.118	EGF+AKTi_S6K	0.180
EGF+AKTi_S6K	0.167	IGF1+MEKi_ERK	0.117	IGF1+MEKi_AKT	-0.179

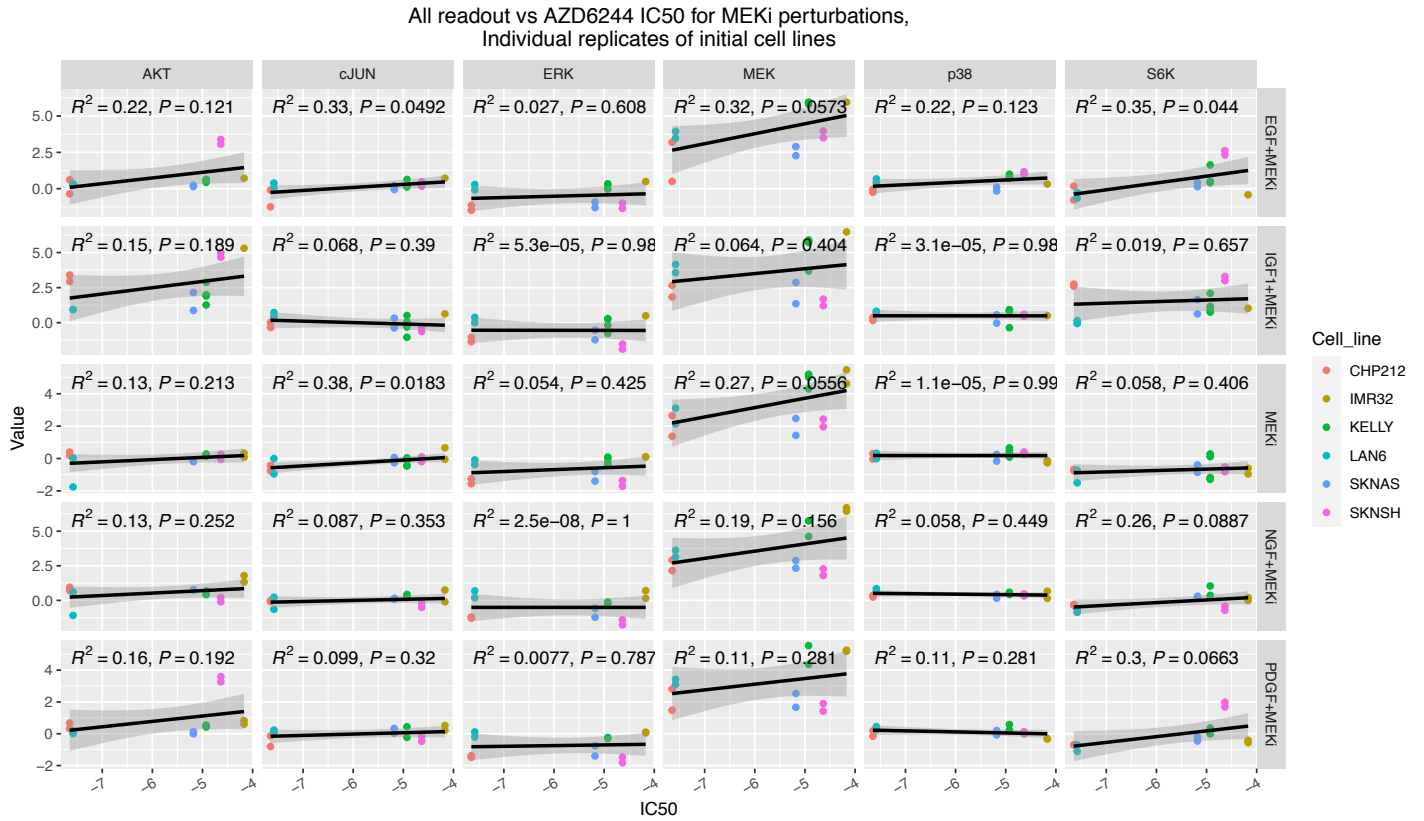
Supplementary Table 1: Main loadings of the first 3 principal components of the perturbation data PCA.



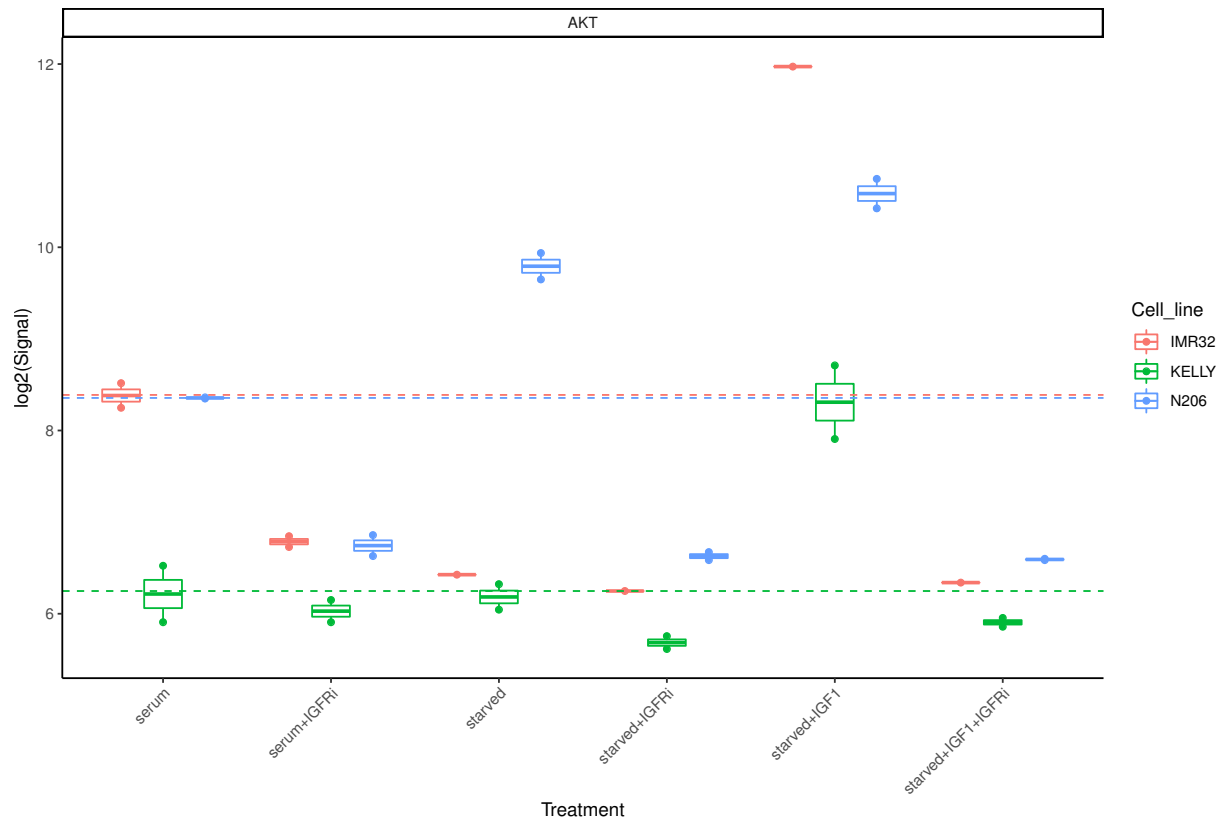
Supplementary Figure 11: Quantile-quantile plots of the initial models using the literature topology (top, initial normal) and the final models after model extension (bottom, best normal).



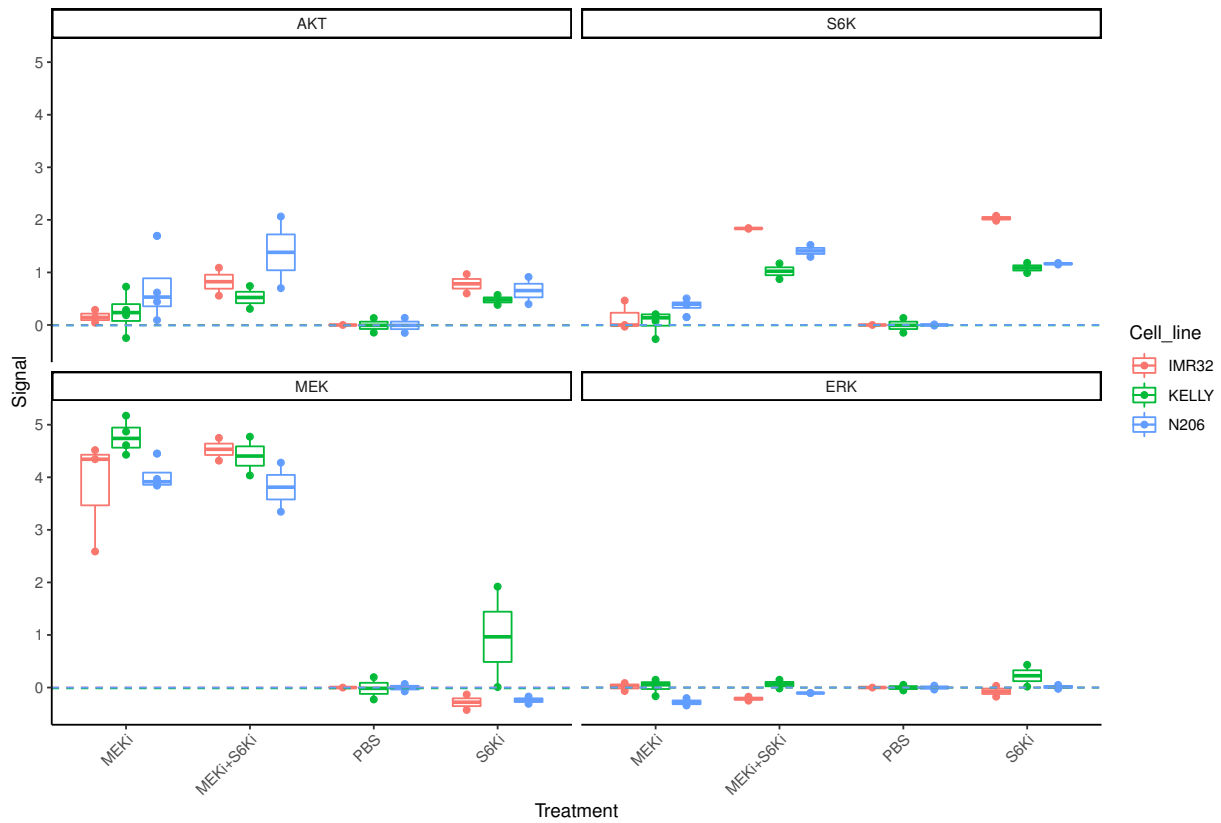
Supplementary Figure 12: Correlation between the fitted path value from ligands to readouts and the expression of the matching receptor or receptor family.



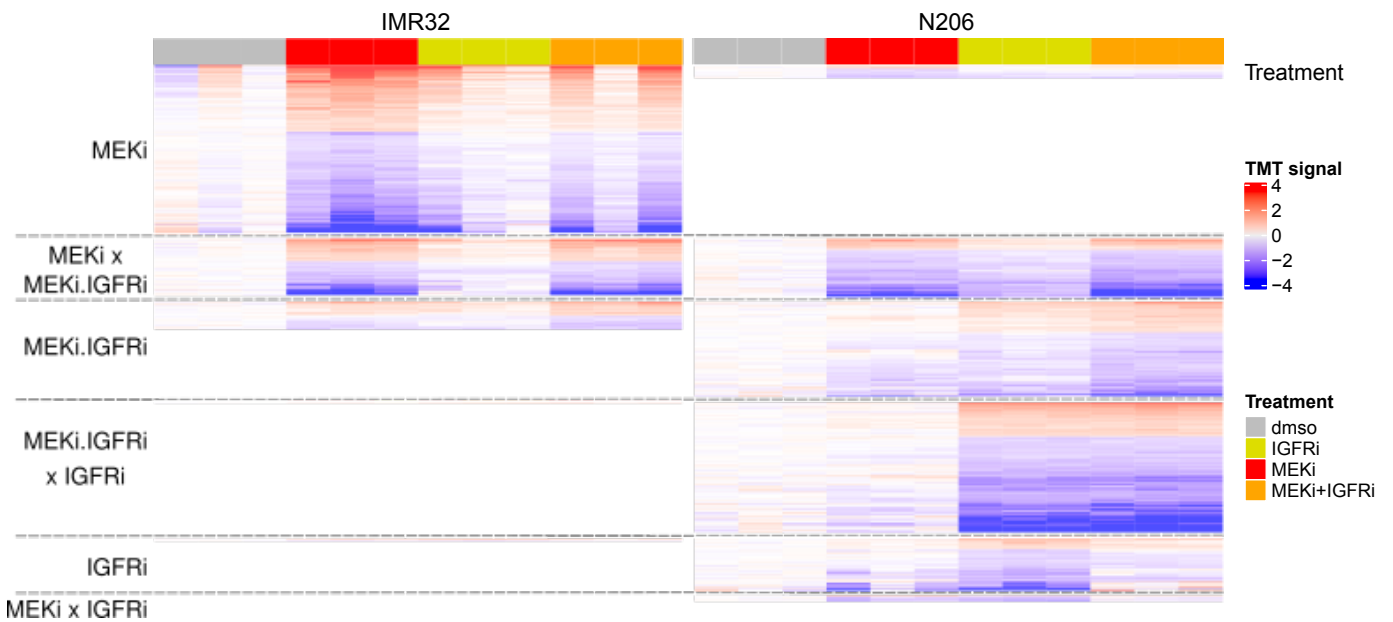
Supplementary Figure 13: AZD6244 IC50 versus responses to perturbations including AZD6244.  $R^2$  and p.value correspond to the linear model shown in black. Points are independent replicates, n=2.



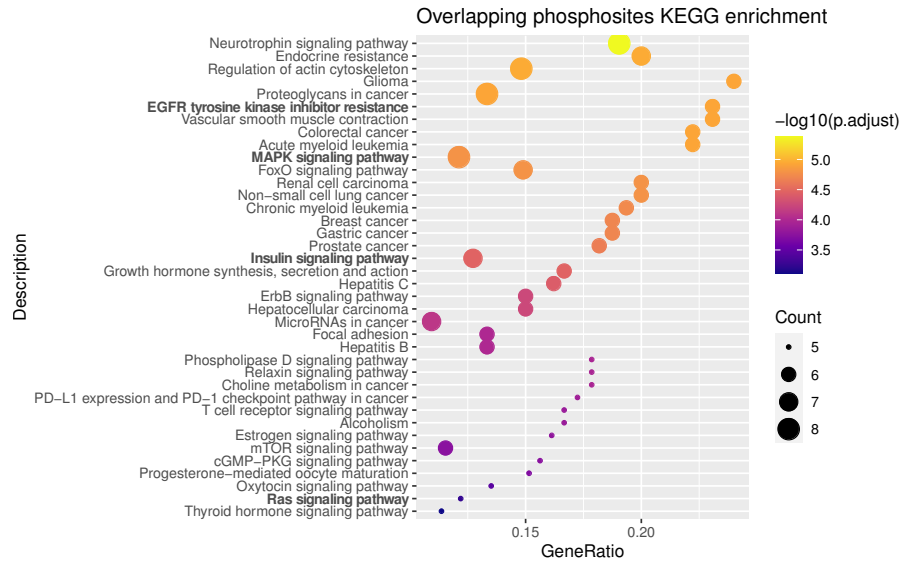
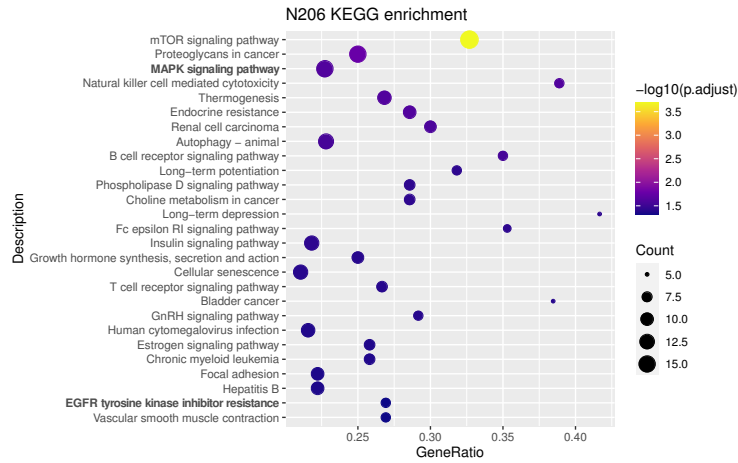
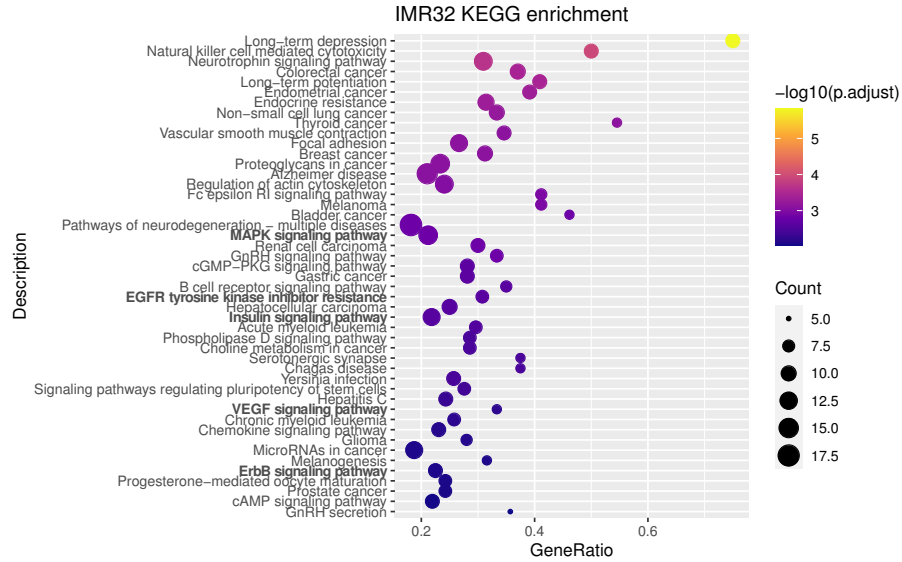
Supplementary Figure 14: Raw plex measurements of pAKT<sup>S473</sup> response to IGFR inhibition under serum, starved or IGF1 condition. The AKT pathway is activated by IGFR in N206 even without serum and is not activated more by IGF1 while IMR32 and KELLY requires IGF1 or other ligands. Dotted line indicates level under serum condition, n=2.



Supplementary Figure 15: PBS normalised plex measurements of p-AKT<sup>S473</sup>, p-ERK<sup>T202/Y204</sup>, p-S6K<sup>T389</sup> and p-MEK<sup>S217/S221</sup>. n=2.



Supplementary Figure 16: Differentially measured phosphopeptides in IMR32 and N206 after 4h inhibition (FDR < 0.05, n=3) classified by the treatment(s) yielding a differential expression.



Supplementary Figure 17: KEGG enrichment of unique genes corresponding to phosphopeptides differentially expressed after MEKi, IGFRi or MEKi+IGFRi treatment in IMR32 (top), N206 (middle) or both strictly (bottom). MAPK related terms are highlighted. Computation using the R package enrichKEGG.