Supplementary Material

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Mapping drug-microenvironment-genetic interplay in CLL reveals trisomy 12 as a modulator of microenvironmental signals

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Supplementary Methods

Drug-stimulation profiling of samples treated with Ibrutinib, IL4 and AS1517499

The experiment in Supp. Fig. 11, was performed as detailed in the main methods (Sample preparation and drug-stimulation profiling), but with the following adjustments. 16 independent CLL PBMC samples were used and luminescence was read out using a Perkin Elmer EnSight.

ATAC sequencing

Peripheral blood was taken from 4 CLL patients and separated by Ficoll gradient (GE Healthcare), mononuclear cells were cryopreserved on liquid nitrogen. Samples were later thawed from frozen as previously described[1] and MACS sorted for CD19 positive cells (Miltenyi autoMACS®). The cells were resuspended in RPMI (GIBCO, Cat.No. 21875–034), with the addition of 2mM glutamine (GIBCO, Cat.No. 25030–24), 1% Pen/Strep (GIBCO, Cat.No. 15140–122) and 10% pooled, heat–inactivated and sterile filtered human type AB male off the clot serum (PAN Biotech, Cat.No. P40–2701, Lot.No:P–020317). 5ml of cell suspension was cultured in 6–well plates (Greiner Bio–One Cat.No. 657160). After thawing, cells were incubated at 37°C and 5% CO2 for 6 hours in 0.2% DMSO. The final cell concentration was 2x10ˆ6 cells/ml. Cell viability and purity was assessed using FACS. All samples had a viability over 90% and over 95% of CD19+/CD5+/CD3– cells.

ATAC sequencing library generation

ATAC-seq libraries were generated as described previously[2]. Cell preparation and transposition was performed according to the protocol, starting with 5x10ˆ4 cells per sample. Purified DNA was stored at −20°C until library preparation was performed. To generate multiplexed libraries, the transposed DNA was initially amplified for 5x PCR cycles using 2.5 L each of 25 M PCR Primer 1 and 2.5 L of 25 M Barcoded PCR Primer 2 (included in the Nextera index kit, Illumina, San Diego, CA, USA), 25 L of NEBNext High-Fidelity 2x PCR Master Mix (New England Biolabs, Boston, Massachusetts) in a total volume of 50 L. 5 L of the amplified DNA was used to determine the appropriate number of additional PCR cycles using qPCR. Additional number of cycles was calculated through the plotting of the linear Rn versus cycle, and corresponds to one-third of the maximum fluorescent intensity. Finally, amplification was performed on the remaining 45 L of the PCR reaction using the optimal number of cycles determined for each library by qPCR (max. 13 cycles in total). The amplified fragments were purified with two rounds of SPRI bead clean-up (1.4x). The size distribution of the libraries was assessed on Bioanalyzer with a DNA High Sensitivity kit (Agilent Technologies, Santa Clara, CA), concentration was measured with Qubit® DNA High Sensitivity kit in Qubit® 2.0 Flurometer (Life Technologies, Carlsbad, CA). Sequencing was performed on NextSeq 500 (Illumina, San Diego, CA, USA) using 75bp paired-end sequencing, generating 450 million paired-reads per run, with an average of 55 million reads per sample.

ATAC sequencing analysis of transcription factor activity in trisomy 12 CLL

Raw ATAC–seq data generated from our CLL samples were processed as described in Berest et al. 2019[3], with the only exception that we did not use CG bias correction step. We then used analytical mode of diffTF with HOCOMOCO v10 database[4] using the following parameters: minOverlap = 1; design formula = "~ Patient + trisomy 12 status".

Drug	Main targets	Target category	Drug Group	Pathway	Distributor	Catalogue number	Conc. 1	Conc. 2
Ibrutinib	BTK	BCR	kinase inhibitor	B-cell receptor	Selleck Chemicals	S2680	500nM	50nM
Idelalisib	PI3K delta	BCR	kinase inhibitor	B-cell receptor	Selleck Chemicals	S2226	500nM	50nM
Fludarabine	Purine analogue	DDR	chemotherapeutic agent	Other	Selleck Chemicals	S1491	2000nM	200nM
Nutlin-3a	MDM2	DDR	other	Other	Selleck Chemicals	S8059	10000nM	1000nM
Selumetinib	MEK1/2	MAPK	kinase inhibitor	Other	Selleck Chemicals	S1008	1000nM	100nM
BAY-11-7085	NFkB	NFkB	other	Other	Selleck Chemicals	S7352	2000nM	200nM
Everolimus	mTOR	mTOR	other	Other	Selleck Chemicals	S1120	500nM	50nM
PRT062607	SYK	BCR	kinase inhibitor	B-cell receptor	Selleck Chemicals	S8032	500nM	50nM
Pyridone-6	JAK1/2/3	JAK/STAT	kinase inhibitor	Other	MedChemExpress	457021-03-7	500nM	50nM
Ralimetinib	p38 MAPK	MAPK	kinase inhibitor	Other	Selleck Chemicals	S1494	1500nM	150nM
Luminespib	HSP90	HSP90	other	Other	Selleck Chemicals	S1069	200nM	20nM
I-BET 762	BRD2/3/4	Epigenome	other	Other	Selleck Chemicals	S7189	1000nM	100nM

Supplementary Table 1: List of drugs, along with their main target, supplier and concentration. All drugs were dissolved in Dimethyl Sulfoxide (DMSO) and stored at –20°C.

Stimulus	Name	Supplier	Concentration	Catalogue Number	Lot Number	Pathway
IL4 human recombinant animal component free	IL4	Sigma-Aldrich	10 ng/ml	SRP3093	0712AFC14	JAK/STAT
IL10 human Animal component free	IL10	Sigma-Aldrich	10 ng/ml	SRP3312	1012AFC21	JAK/STAT
IL2 human recombinant animal component free	IL2	Sigma-Aldrich	10 ng/ml	SRP3085	0416AFC12	JAK/STAT
R-848	Resiquimod	Enzo Life Siences	1000 ng/ml	ALX-420-038-M025	10211615	TLR 7/8
Human IL-21	IL21	Peprotech	10 ng/ml	200-21	414226	JAK/STAT
Human BAFF	BAFF	Peprotech	250 ng/ml	310-13	0706CY194	NFkB
Human IL-1	IL1	Peprotech	10 ng/ml	200-01	0606B95	NFkB
Human sCD40 Ligand	sCD40L	Peprotech	1000 ng/ml	310-02	1214145	NFkB
Goat F(AB')2 Fragment to human IgM	soluble anti-IgM	MP Biomedicals	20000 ng/ml	55055	7227	BCR
Human TGF 1	TGF 1	Peprotech	10 ng/ml	100-21	1117209	MAPK
Human IL15	IL15	Peprotech	10 ng/ml	200-15	91624	JAK/STAT
Human IL6	IL6	Peprotech	10 ng/ml	200-06	031316-2	JAK/STAT
ODN 2006 (ODN 7909)	CpG ODN	Invivogen	1000 ng/ml	tlrl-2006-1	3901-09T	TLR 9
Human SDF1 (CXCL12)	SDF-1	Peprotech	200 ng/ml	300-28A	101492	JAK/STAT
Human Interferon	Interferon	Peprotech	5 ng/ml	300-02	121527	NFkB
HS-5 konditioniertes Medium	HS-5 CM	self produced	20 %	NA	NA	NA

Supplementary Table 2: List of used microenvironmental stimuli, Supplier, concentration and main pathway.

Patient ID	Sex	Treated before	IGHV status	Methylation Cluster	Del13q	Del11q	Trisomy 12	Del17p
Pat_001	f	1	U	LP	1	0	0	0
Pat_002	m	1	M	IP	1	0	0	0
Pat_003	m	0	M	HP	0	0	1	0
Pat_004	f	1	U	LP	0	1	0	0
Pat_005	m	0	U	LP	1	0	0	0
Pat_006	f	0	U	LP	0	0	0	0
Pat_007	f	0	M	HP	1	0	0	0
Pat_008	m	1	U	LP	1	0	0	0
Pat_009	m	1	U	LP	1	0	0	1
Pat_010	f	1	U	LP	1	0	0	1
Pat_011	f	0	U	NA	0	0	1	0
Pat_012	f	0	M	HP	1	0	0	0
Pat_013	f	1	U	IP	1	1	0	0
Pat_014	m	0	M	HP	0	0	0	0
Pat_015	m	0	M	HP	1	0	0	0
Pat_016	m	0	M	HP	1	0	0	0
Pat_017	m	0	M	NA	1	0	0	0
Pat_018	f	1	U	LP	1	1	0	0
Pat_019	m	0	M	HP	1	0	0	0
Pat_020	f	1	M	IP	1	0	0	0
Pat_021	m	0	U	LP	0	0	0	1
Pat_022	f	0	M	IP	0	0	1	0
Pat_023	f	0	M	HP	0	0	0	0
Pat_024	f	1	M	HP	0	0	0	1
Pat_025	m	0	M	IP	1	0	0	0
Pat_026	m	0	M	HP	1	0	0	0
Pat_027	f	0	M	HP	1	0	0	0
Pat_028	f	0	M	IP	1	0	0	0
Pat_029	f	0	M	HP	1	0	0	0
Pat_030	m	1	M	HP	1	0	0	0
Pat_031	m	0	M	HP	0	0	0	0
Pat_032	f	1	U	LP	1	1	0	0
Pat_033	m	1	U	IP	0	1	0	0
Pat_034	m	1	U	LP	0	1	0	0
Pat_035	m	0	M	HP	1	0	0	0
Pat_036	m	1	U	LP	1	1	0	1
Pat_037	f	1	U	IP	1	0	0	0
Pat_038	m	0	M	IP	1	0	0	0
Pat_039	m	1	M	HP	1	0	0	0
Pat_040	f	0	M	HP	0	0	0	0
Pat_041	f	1	U	LP	0	0	1	0
Pat_042	f	0	M	IP	1	1	0	0
Pat_043	f	0	M	HP	1	0	0	0
Pat_044	m	0	M	HP	1	0	0	0
Pat_045	m	0	U	LP	0	0	0	0
Pat_046	m	0	M	IP	0	0	1	0
Pat_047	m	0	M	HP	1	0	0	0
Pat_048	m	0	M	HP	1	0	0	0
Pat_049	f	0	M	IP	0	1	0	0
Pat_050	m	0	M	HP	0	0	1	0
Pat_051	m	0	M	NA	1	0	0	0
Pat_052	f	0	M	IP	1	0	0	0
Pat_053	m	1	U	LP	1	1	0	0
Pat_054	f	1	U	LP	0	1	0	0
Pat_055	m	1	U	LP	0	0	0	0
Pat_056	f	0	U	LP	NA	NA	NA	NA
Pat_057	f	0	M	HP	1	0	1	0
Pat_058	f	1	U	LP	0	0	0	0
Pat_059	m	0	M	HP	1	0	0	0
Pat_060	m	1	M	IP	1	0	0	1
Pat_061	m	0	U	LP	0	0	1	0

(continued)

Patient ID	Sex	Treated before	IGHV status	Methylation Cluster	Del13q	Del11q	Trisomy 12	Del17p
Pat_062	m	1	U	LP	1	1	0	0
Pat_063	f	0	U	LP	1	0	0	0
Pat_064	m	1	U	LP	1	1	0	1
Pat_065	m	0	U	LP	0	1	0	0
Pat_066	m	1	U	LP	1	1	0	0
Pat_067	f	0	M	HP	1	0	0	0
Pat_068	m	0	M	HP	1	0	0	0
Pat_069	m	1	M	HP	1	0	0	0
Pat_070	f	0	M	HP	0	0	0	0
Pat_071	f	0	U	LP	0	0	0	0
Pat_072	m	1	M	HP	0	0	1	0
Pat_073	f	0	U	LP	1	1	0	0
Pat_074	f	0	M	HP	0	0	0	0
Pat_075	f	0	M	HP	1	0	0	0
Pat_076	m	0	M	HP	1	0	0	0
Pat_077	f	0	U	NA	0	0	1	0
Pat_078	m	0	U	LP	0	0	0	0
Pat_079	m	0	M	HP	1	0	0	0
Pat_080	f	0	M	HP	0	0	0	0
Pat_081	m	0	M	HP	0	0	0	0
Pat_082	m	0	U	LP	0	0	0	0
Pat_083	m	0	M	HP	0	0	0	0
Pat_084	m	0	U	LP	0	0	1	0
Pat_085	m	0	M	HP	0	0	0	0
Pat_086	m	1	U	LP	1	1	0	0
Pat_087	m	0	M	IP	1	0	0	0
Pat_088	f	1	U	LP	1	0	0	1
Pat_089	m	0	M	HP	0	0	0	0
Pat_090	m	1	U	LP	0	0	1	0
Pat_091	m	1	M	NA	1	0	0	0
Pat_092	m	1	M	HP	0	0	0	0
Pat_093	m	0	M	HP	1	0	0	0
Pat_094	f	1	M	HP	0	0	0	0
Pat_095	m	1	U	LP	0	0	0	0
Pat_096	m	0	M	HP	0	0	0	0
Pat_097	f	1	U	LP	0	0	0	0
Pat_098	m	0	M	HP	1	0	0	0
Pat_099	f	0	U	LP	1	0	0	0
Pat_100	f	0	U	LP	1	0	0	0
Pat_101	f	0	U	LP	1	0	0	0
Pat_102	m	1	U	IP	0	0	0	0
Pat_103	f	0	M	HP	1	0	1	0
Pat_104	f	1	M	HP	0	0	0	0
Pat_105	m	0	U	LP	NA	NA	NA	NA
Pat_106	m	0	U	LP	1	1	0	1
Pat_107	f	0	M	NA	1	0	0	0
Pat_108	m	0	M	NA	1	0	1	0
Pat_109	m	0	M	HP	1	0	0	0
Pat_110	m	0	M	IP	1	1	0	0
Pat_111	f	1	U	LP	1	0	0	0
Pat_112	f	0	M	NA	0	0	1	0
Pat_113	f	0	M	HP	1	0	0	0
Pat_114	m	0	U	LP	1	0	0	0
Pat_115	m	1	U	LP	1	0	0	1
Pat_116	m	0	U	LP	1	0	0	0
Pat_117	m	0	U	IP	1	0	0	0
Pat_118	f	0	M	HP	0	0	0	1
Pat_119	m	0	U	LP	NA	NA	NA	NA
Pat_120	f	0	U	LP	0	0	1	0
Pat_121	m	0	U	LP	0	0	0	1

(continued)

Patient ID	Sex	Treated before	IGHV status	Methylation Cluster	Del13q	Del11q	Trisomy 12	Del17p
Pat_122	m	0	U	LP	0	1	0	0
Pat_123	m	0	U	LP	1	0	0	1
Pat_124	f	0	M	HP	1	0	1	0
Pat_125	f	0	M	HP	1	0	0	0
Pat_126	m	1	NA	NA	0	0	1	0
Pat_127	m	0	U	LP	1	1	0	1
Pat_128	m	0	M	HP	1	0	0	0
Pat_129	m	1	U	LP	1	0	0	0
Pat_130	f	0	M	IP	1	0	0	0
Pat_131	f	0	U	LP	1	0	0	1
Pat_132	m	1	U	LP	1	0	0	1
Pat_133	m	1	U	LP	1	0	0	1
Pat_134	m	1	M	HP	1	0	0	1
Pat_135	m	0	M	HP	1	0	0	0
Pat_136	m	0	M	HP	1	0	0	0
Pat_137	f	0	U	LP	0	0	1	0
Pat_138	f	0	M	HP	1	0	0	0
Pat_139	f	0	M	HP	NA	NA	NA	NA
Pat_140	f	0	M	IP	1	0	0	0
Pat_141	m	0	M	IP	1	0	0	0
Pat_142	m	0	M	HP	1	0	0	0
Pat_143	f	0	U	LP	1	0	0	0
Pat_144	m	1	U	LP	0	0	0	1
Pat_145	f	0	M	HP	0	0	0	0
Pat_146	m	1	U	LP	NA	NA	NA	NA
Pat_147	m	1	U	LP	0	0	0	1
Pat_148	m	1	U	NA	1	0	0	0
Pat_149	m	1	U	LP	0	1	1	0
Pat_150	f	0	M	HP	1	0	0	NA
Pat_151	m	0	U	LP	0	0	1	0
Pat_152	m	0	NA	NA	0	1	1	0
Pat_153	m	1	U	LP	1	0	0	0
Pat_154	m	0	M	HP	1	0	0	0
Pat_155	m	0	M	HP	1	0	0	0
Pat_156	f	0	U	LP	1	0	0	0
Pat_157	f	0	U	LP	1	1	0	0
Pat_158	m	0	M	HP	1	0	0	0
Pat_159	f	0	U	LP	1	0	0	0
Pat_160	m	0	U	LP	NA	NA	NA	NA
Pat_161	m	1	U	LP	0	0	0	0
Pat_162	m	0	M	HP	0	0	0	0
Pat_163	m	0	M	HP	0	0	0	0
Pat_164	f	0	U	LP	0	0	0	0
Pat_165	m	1	U	LP	0	1	1	0
Pat_166	m	0	U	LP	1	0	1	0
Pat_167	m	0	NA	IP	NA	NA	NA	NA
Pat_168	m	0	M	HP	1	1	0	0
Pat_169	m	0	M	HP	0	0	1	0
Pat_170	m	0	M	HP	1	0	0	0
Pat_171	m	0	M	HP	1	0	0	0
Pat_172	m	0	M	HP	1	0	0	0
Pat_173	m	0	M	HP	1	0	0	0
Pat_174	f	0	U	LP	NA	0	NA	0
Pat_175	m	0	U	LP	0	0	0	0
Pat_176	f	0	M	HP	NA	NA	NA	NA
Pat_177	f	0	NA	IP	NA	1	NA	NA
Pat_178	m	0	M	HP	1	0	0	0
Pat_179	m	0	U	LP	0	1	0	0
Pat_180	m	0	M	HP	NA	NA	NA	NA
Pat_181	f	0	M	HP	NA	NA	NA	NA

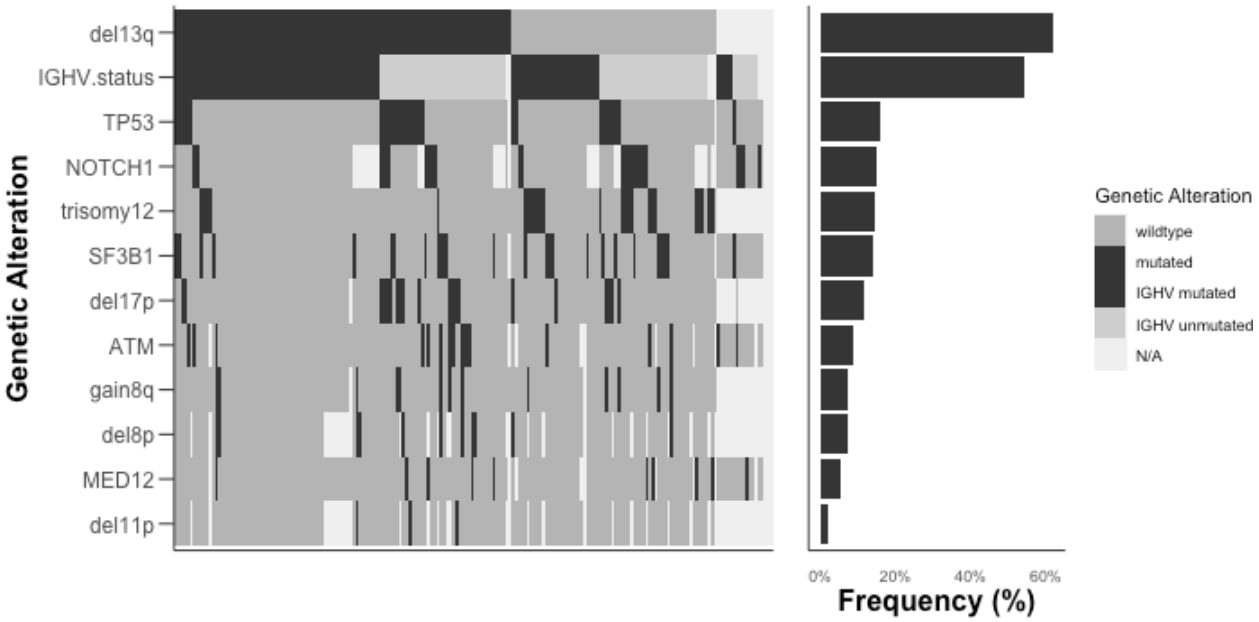
(continued)

Patient ID	Sex	Treated before	IGHV status	Methylation Cluster	Del13q	Del11q	Trisomy 12	Del17p
Pat_182	m	0	M	HP	1	0	0	0
Pat_183	f	1	NA	IP	1	0	0	0
Pat_184	m	0	U	LP	NA	NA	NA	NA
Pat_185	m	0	M	HP	NA	NA	NA	NA
Pat_186	m	0	M	HP	1	0	0	0
Pat_187	m	1	U	LP	NA	NA	NA	NA
Pat_188	m	0	NA	NA	NA	NA	NA	NA
Pat_189	m	0	NA	NA	NA	NA	NA	NA
Pat_190	m	0	NA	NA	NA	NA	NA	NA
Pat_191	f	0	NA	NA	0	0	0	0
Pat_192	f	0	NA	NA	1	0	0	0

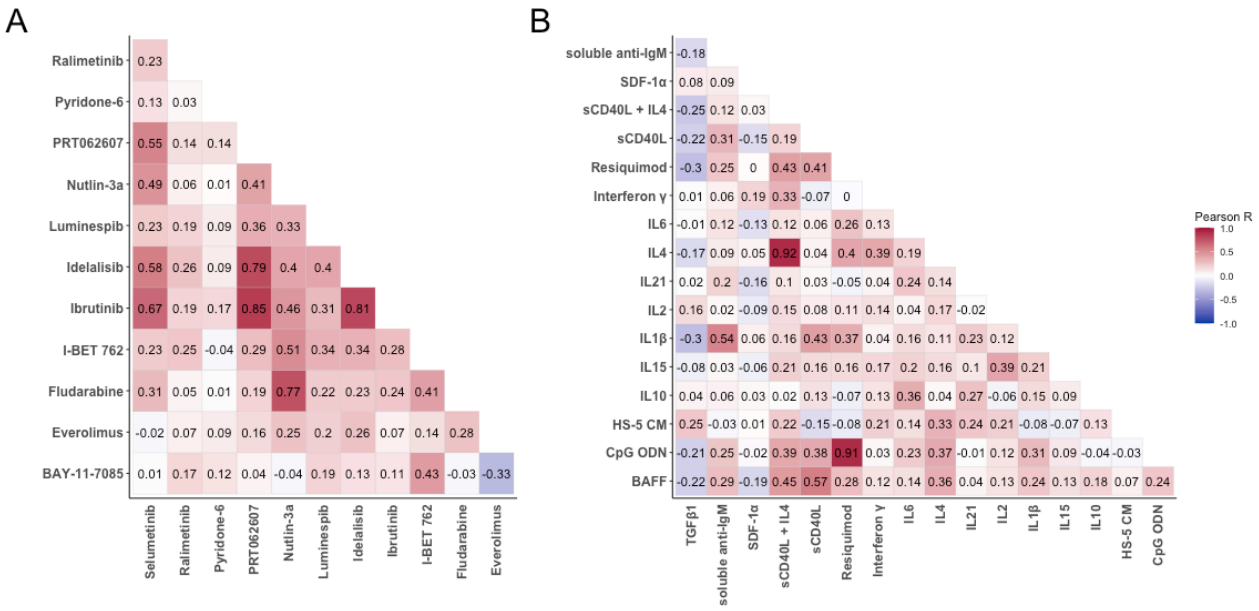
Supplementary Table 3: List of included patients and selected characteristics. For a full list of characteristics see online vignette.

Factor	coef	exp(coef)	se(coef)	z	p.value
Cluster 3 vs Cluster 1	-0.03979	0.96099	0.29813	-0.13347	0.89382
Cluster 3 vs Cluster 2	0.51595	1.67522	0.37741	1.36708	0.1716
Cluster 3 vs Cluster 4	-0.82011	0.44038	0.39760	-2.06267	0.03914
IGHV.status	0.55192	1.73658	0.27253	2.02513	0.04285
trisomy 12	-0.13357	0.87496	0.35617	-0.37503	0.70764
TP53	1.38977	4.01395	0.26072	5.33058	<0.0001

Supplementary Table 4: Multivariate Cox proportional hazards model of stimuli and genetic subgroups of disease progression using C3 as reference.



Supplementary Figure 1: Genetic profiles of screened patient samples. Selected genetic alterations on y-axis and screened patient samples on x-axis.



Supplementary Figure 2: Pearson correlation of log transformed viability values normalised to untreated control. Correlation between drug treatments **(A)** and microenvironmental stimuli **(B)**.

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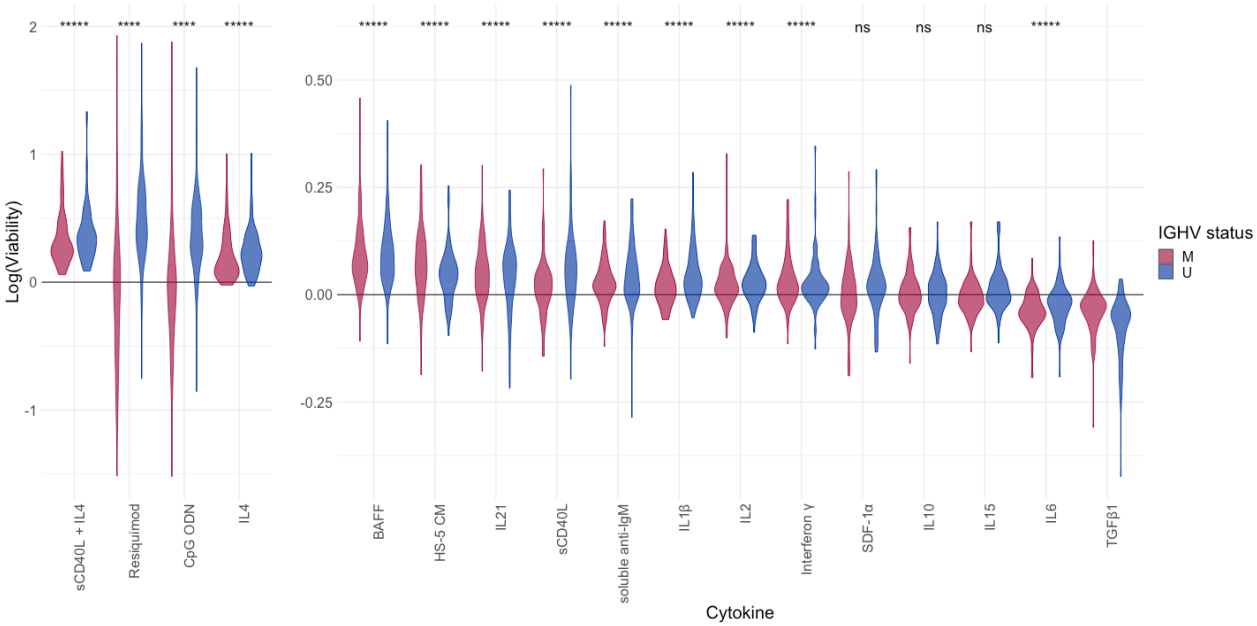

Supplementary Figure 3: Log transformed viabilities, normalised to DMSO controls, after treatment with each stimulus, stratified by IGHV status. BH-adjusted p-values are shown from one-sample t-tests (p<0.00001=*****, p<0.0001=****, p>0.05=ns)

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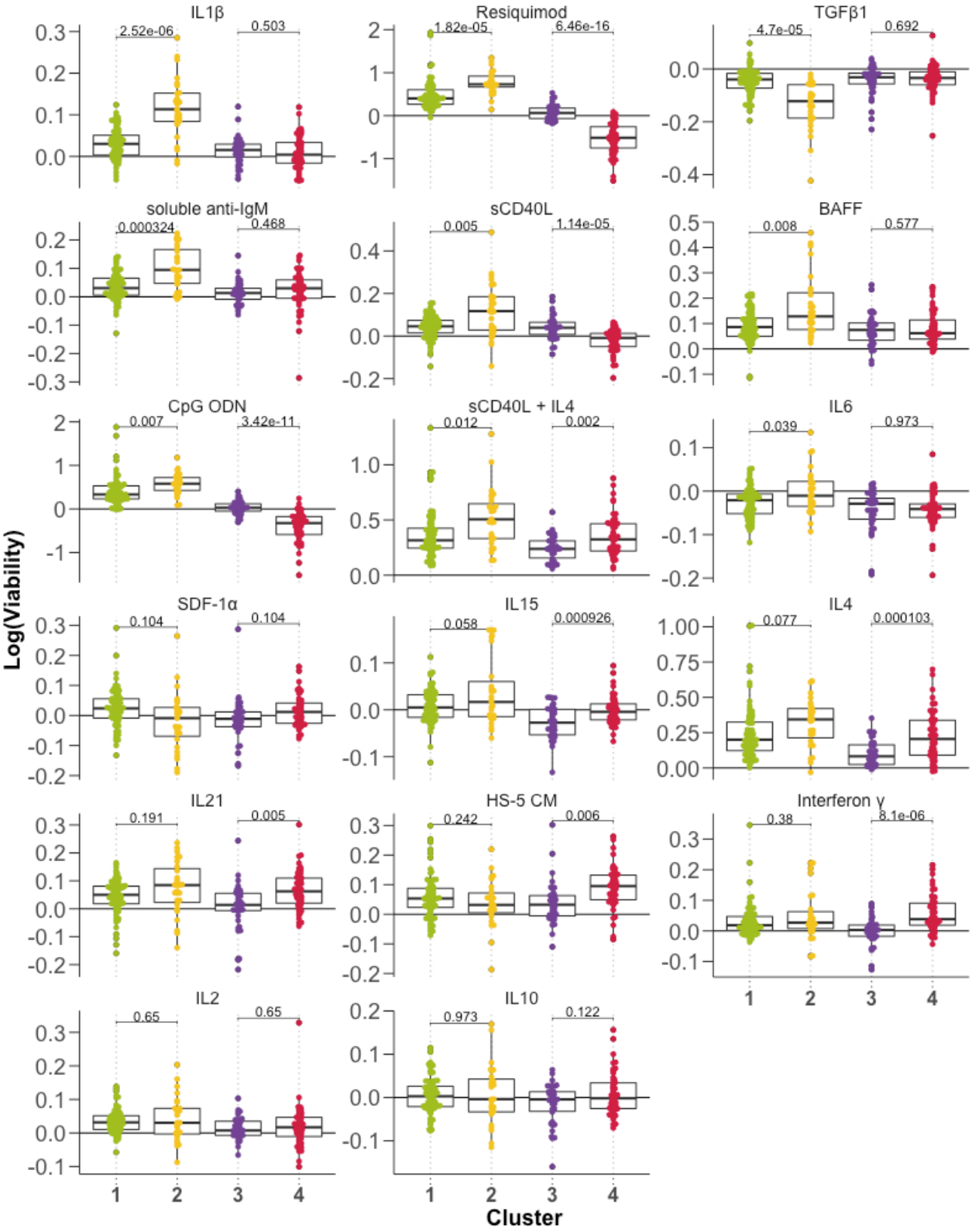
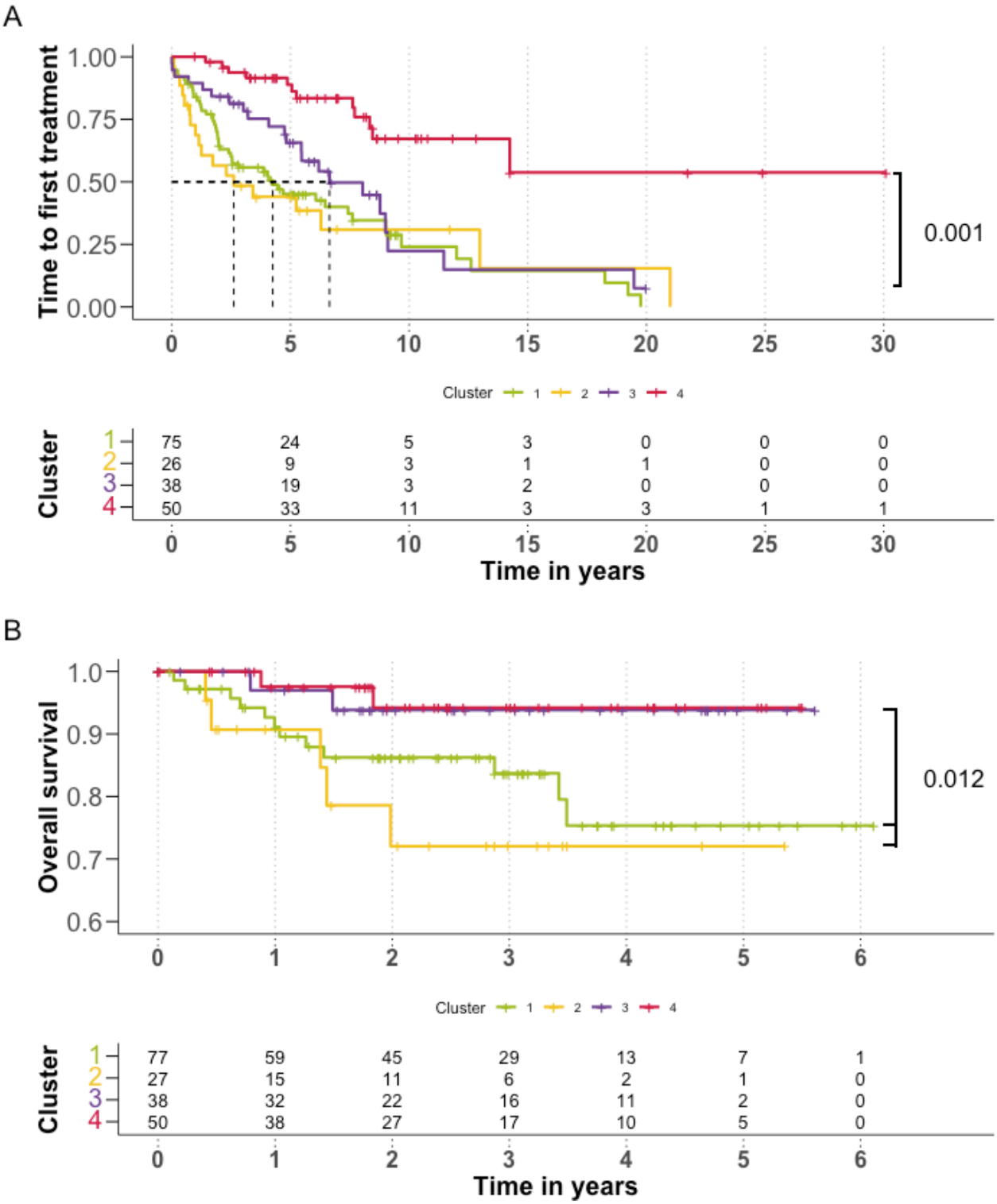
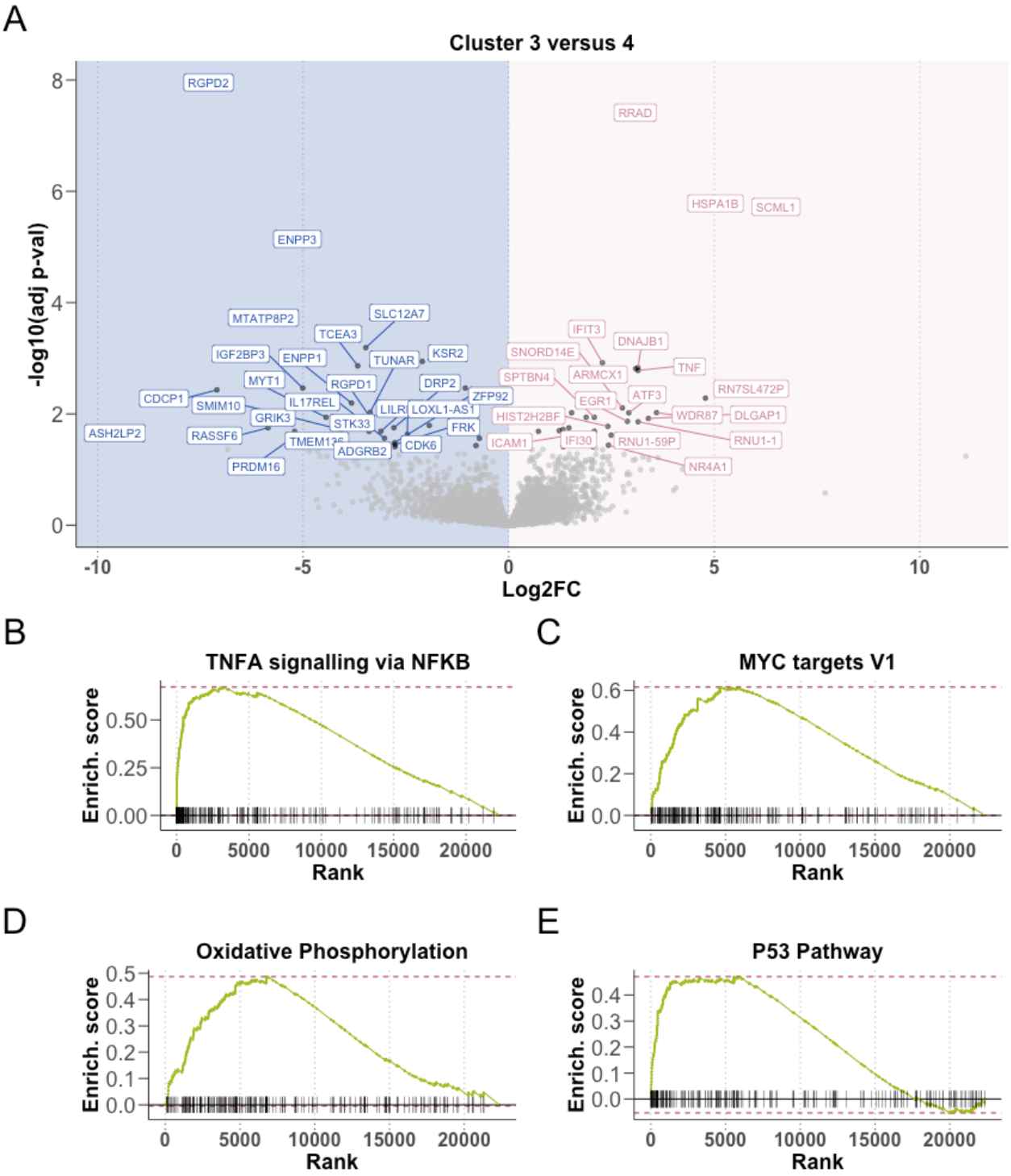


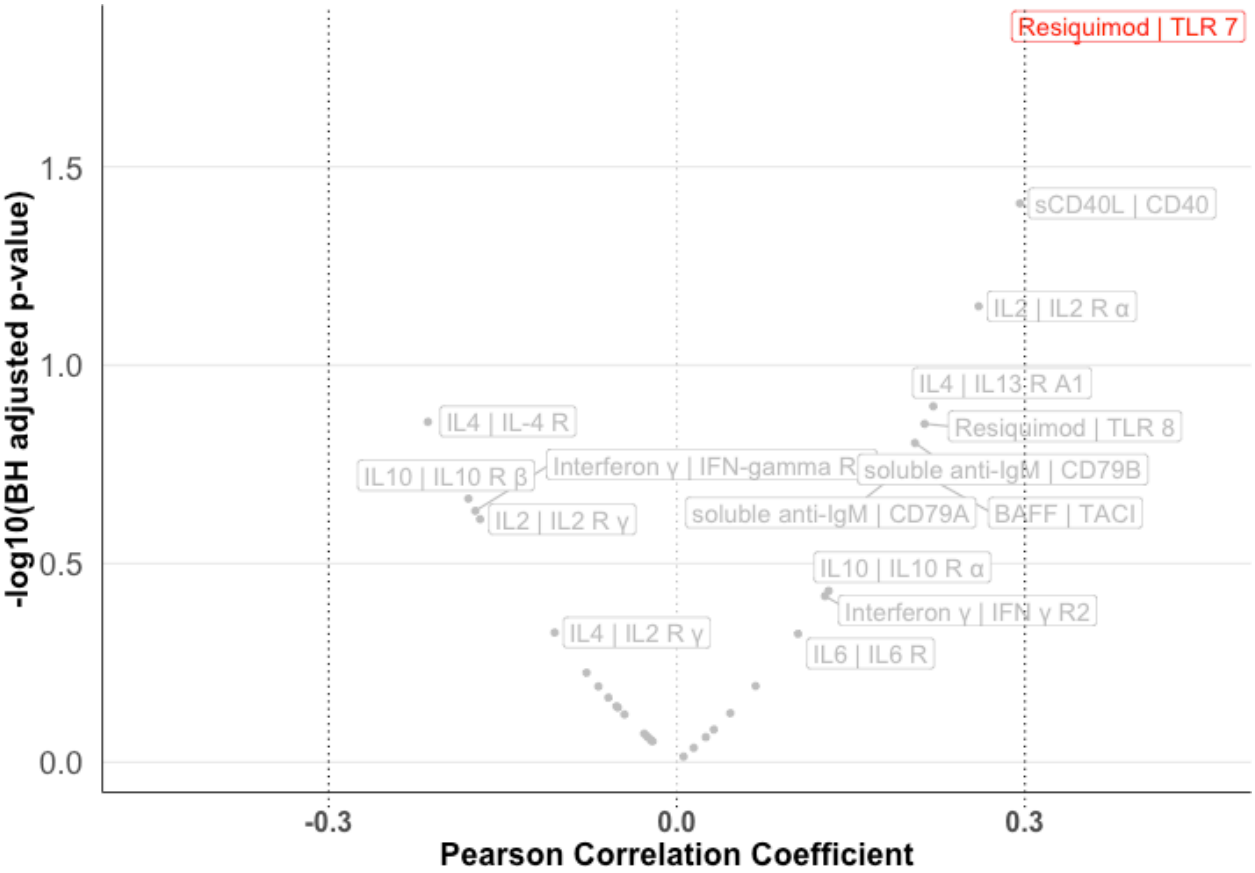
Supplementary Figure 4: Log transformed viabilities after treatment with stimuli, faceted by cluster. BH-adjusted p-values from student's t-tests are shown.



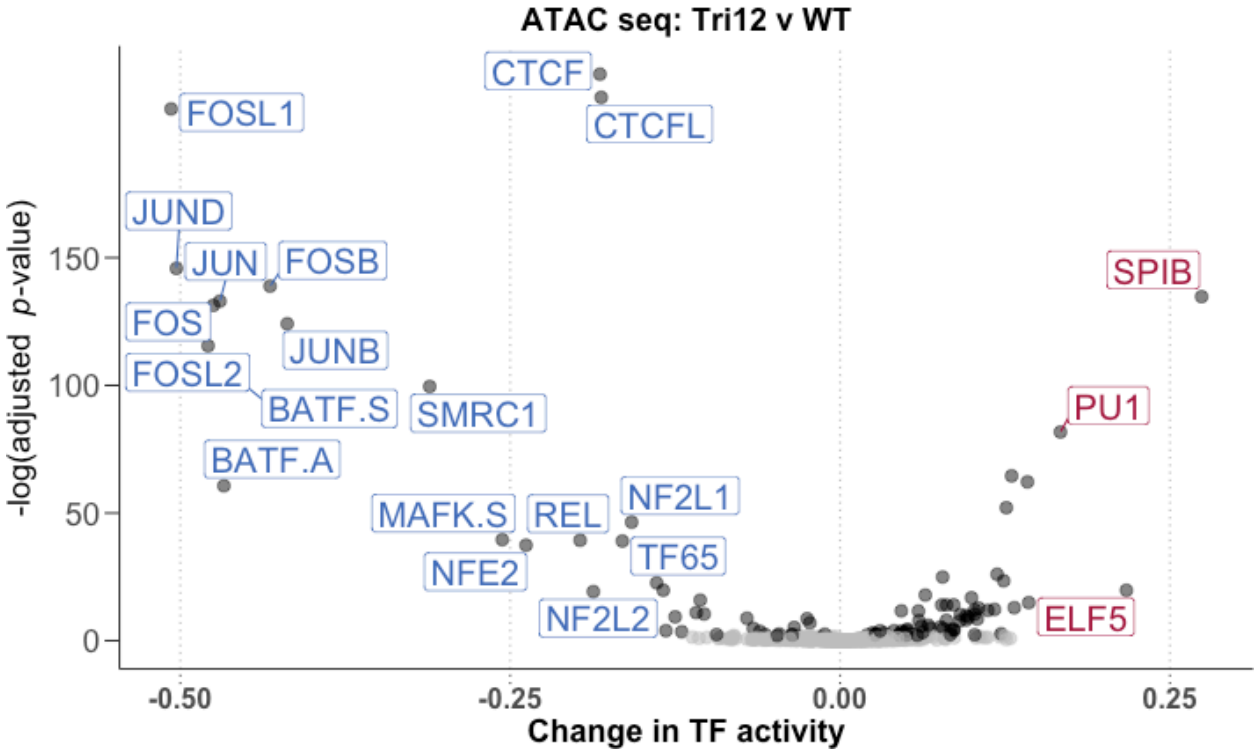
Supplementary Figure 5: Kaplan-Meier Curves of overall survival with p-value from univariate Cox proportional hazards model between C1&2 and C3&4 **(A)** and time to first treatment with p-value from univariate Cox proportional hazards model between C3 and C4 **(B)**. Median survival not reached.



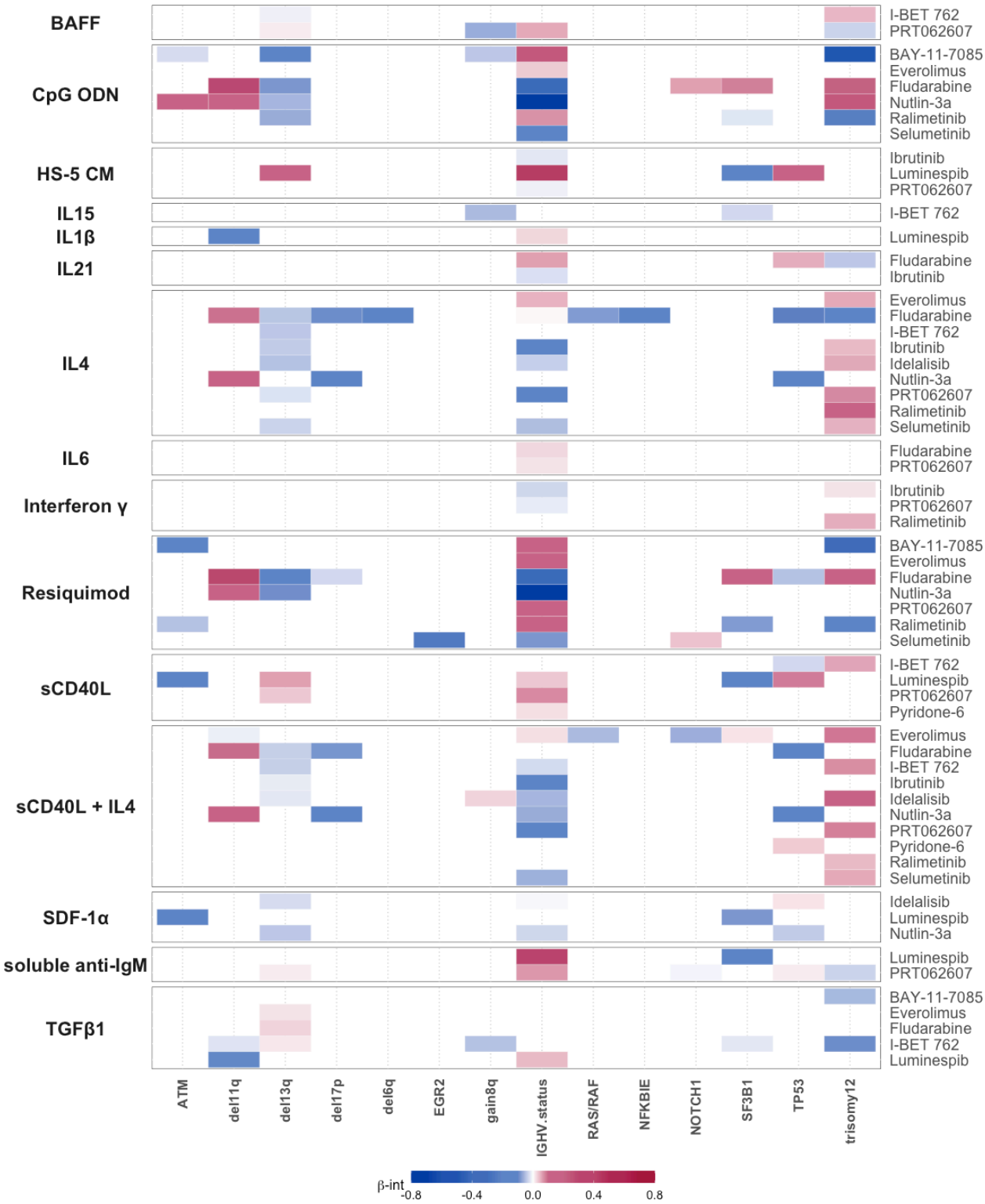
Supplementary Figure 6: RNA-Sequencing of matched samples indicates differential gene expression between Cluster 3 and Cluster 4. **(A)** Volcano plot of differentially expressed genes between Cluster 3 and Cluster 4. X axis indicates log2 fold change values, calculated using the Deseq package, y axis gives corresponding -log10(adjusted p value). P values adjusted using BH method. Genes are labeled where p value < 0.05. **(B-D)** Enrichment plots of selected pathways. Gene set enrichment analysis (GSEA) was performed with the Hallmark gene sets from the GSEA Molecular Signatures Database. Wald statistic was used to rank the genes. The green curve corresponds to the Enrichment Score curve, which is the running sum of the weighted enrichment score obtained from GSEA software.



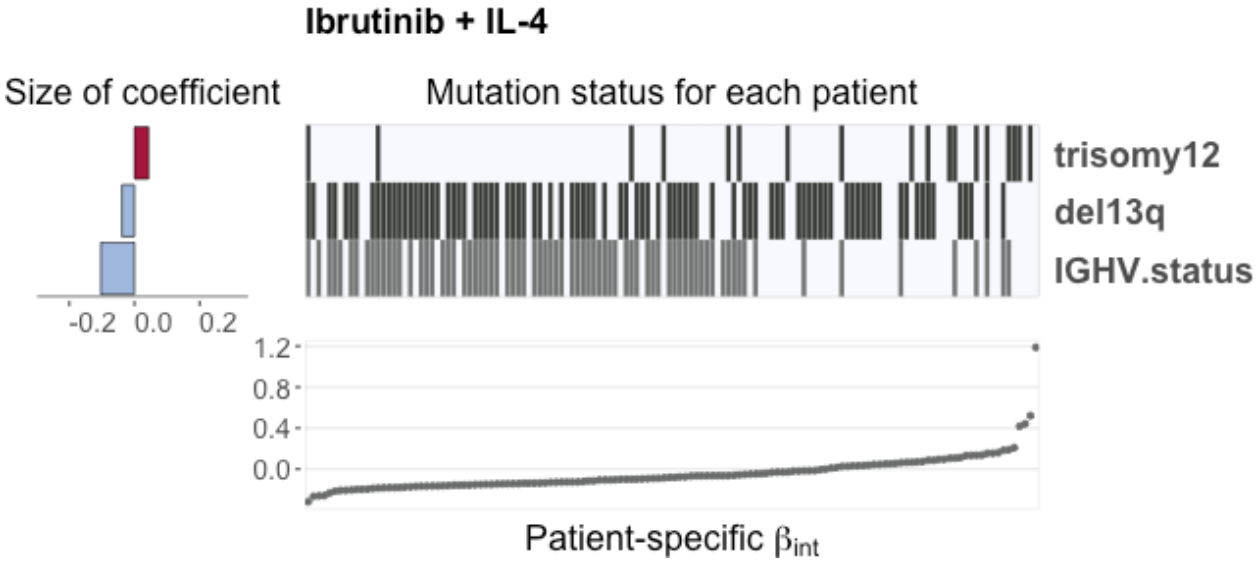
Supplementary Figure 7:
The effects of the microenvironmental stimuli on viability were largely independent of the expression of the corresponding stimuli receptors. Volcano plot depicts Pearson correlation coefficients against corresponding BH-adjusted p values, for the correlation between control - normalised log viability values with each stimulus and vst RNA counts of corresponding stimuli receptor. RNA counts taken from RNA-Sequencing of untreated matched CLL patient sample. Only viability after treatment with Resiquimod correlated with receptor expression (R>0.3).



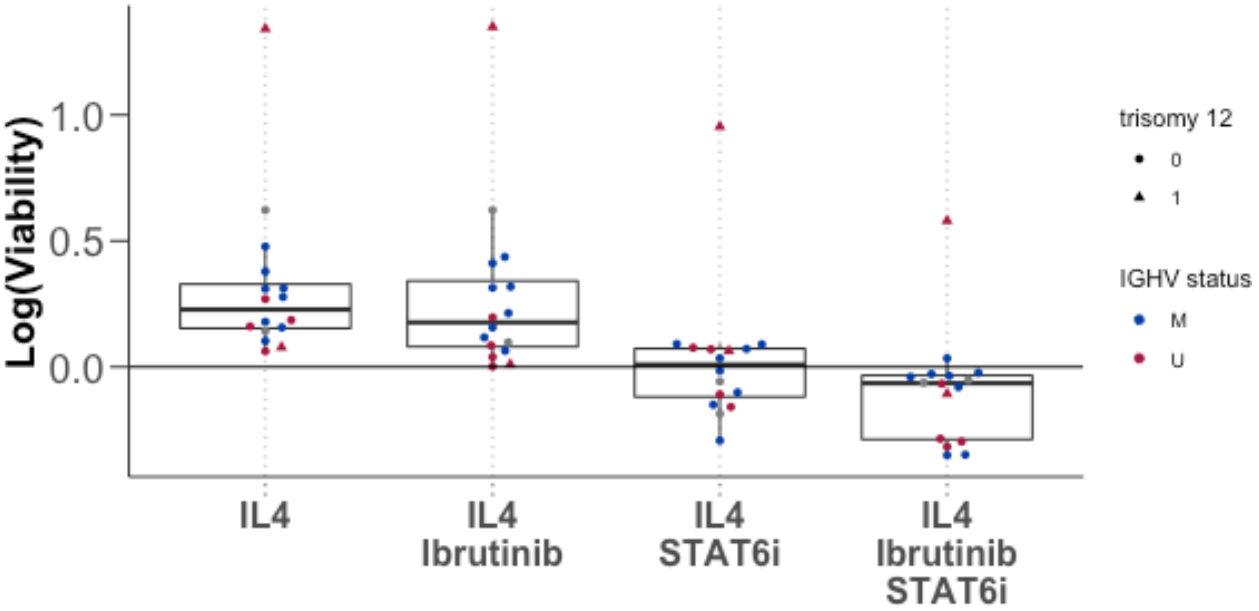
Supplementary Figure 8: Volcano plot shows change in TF activity (x axis) against adjusted p-values (y axis) for trisomy 12 (n = 2) versus non-trisomy 12 samples (n = 2) for 636 TFs. TF activity calculated using the diffTF package, and measured as weighted mean difference. p-values are obtained through diffTF in analytic mode and adjusted by the Benjamini-Hochberg procedure. TFs are labeled where absolute weighted mean difference > 0.15, and adjusted p-value < 0.01.



Supplementary Figure 9: Heatmap depicting overview of genetic predictors of drug - stimulus interactions (each row represents the coefficients from fitting a single multivariate model). Stimuli are shown on left, and corresponding drugs on right. Drugs, stimuli and genetic alterations are alphabetically sorted. Coloured fields indicate that the $\theta 3B21_{\text{int}}$ for given drug and stimulus is modulated by corresponding genetic feature. Positive coefficients are shown in red, indicating $\theta 3B21_{\text{int}}$ is more positive for given drug and stimulus combination if the feature is present.



Supplementary Figure 10: Predictor profile depicting genetic features that modulate the size of β_{int} for ibrutinib and IL-4. To generate predictor profile, linear model in Eqn. (1) was fitted in a sample - specific manner, to calculate drug-stimulus interaction coefficients (β_{int})for each patient sample. Ranked patient-specific β_{int} values are shown in lower scatter plot. Associations between the size of β_{int} and genetic features were identified using multivariate regression with L1 (lasso) regularisation, with gene mutations and IGHV status as predictors,and selecting coefficients that were chosen in >90% of bootstrapped model fits. The horizontal bars on left show the size of fitted coefficients assigned to genetic features. Matrix above scatter plot indicates patient mutation status for the selected genetic features. Matrix fields correspond to points in scatter plot (ie patient data is aligned), to indicate how the size of β_{int} varies with selected genetic feature.



Supplementary Figure 11: The effects observed with IL4 stimulation are dependent on STAT6 activation. Addition of the STAT6 inhibitor AS1517499 could revoke the effect on baseline viability as well as drug induced toxicity. Log transformed viability after treatment with IL4 in combination with ibrutinib, the STAT6 inhibitor AS1517499, and both.

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