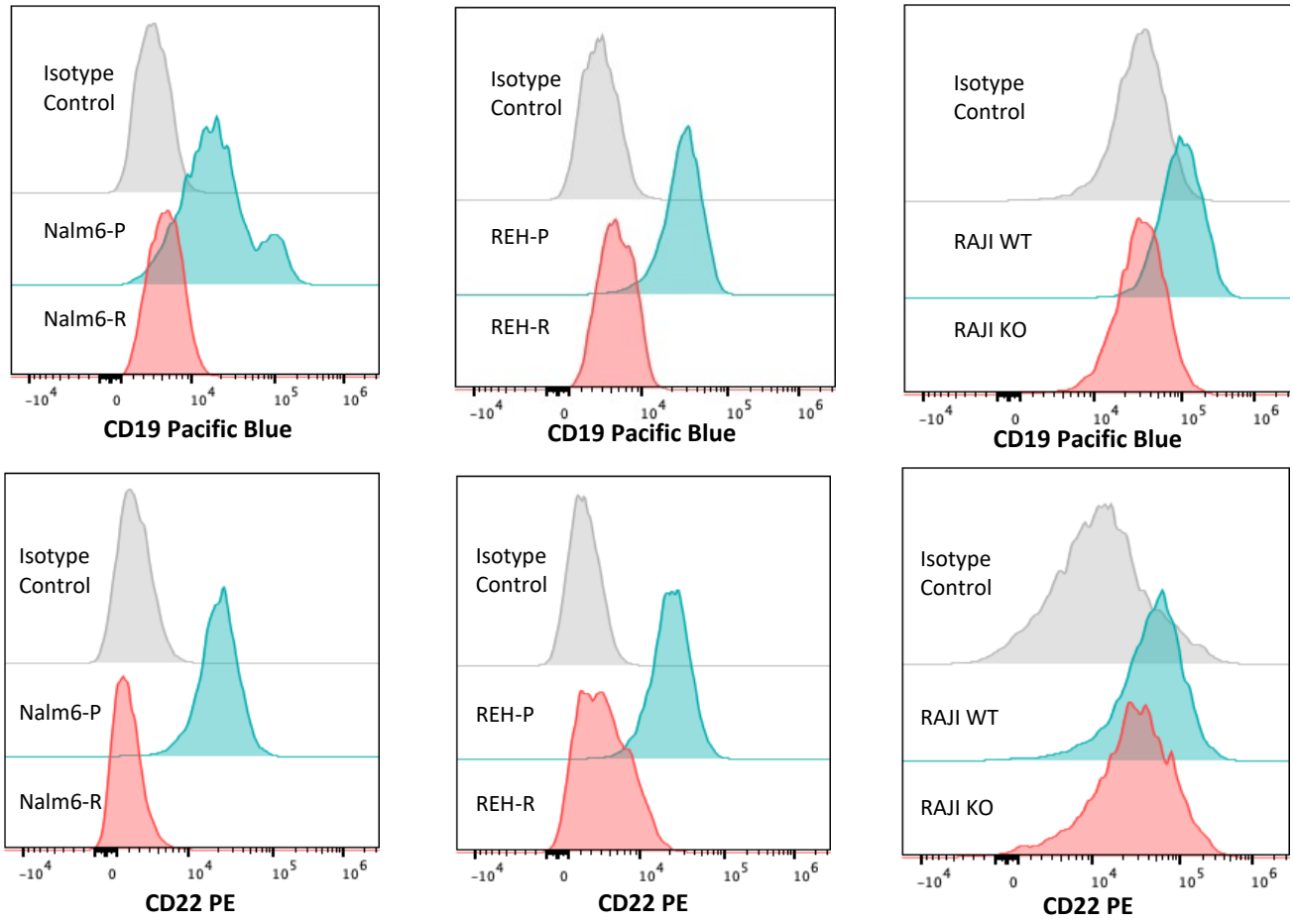


Supplementary Fig 1: CD19 and CD22 flow cytometry with isotype controls for Nalm6 and REH parental and resistant cells as well as RAJI WT and CD19 KO cells.

CyTOF Mass Cytometry Panel			
Target	Clone	Source	Isotope
CD19	HIB19	Biolegend	Nd142
CD20	2H7	Biolegend	Sm147
p4E-BP1	236B4	Cell Signaling	Sm149
pp38	D3F9	Fluidigm	Gd156
CD5	UCHT2	Biolegend	Gd158
pMAPKAP2	27B7	Fluidigm	Tb159
pPLCg2	K86–689.37	Fluidigm	Dy162
pCREB	87G3	Fluidigm	Ho165
CD3	UCHT1	Biolegend	Er168
CD22	HIB22	Biolegend	Tm169
pERK1_2	D13.14.4E	Fluidigm	Yb171
HLADR	L243	Biolegend	Yb174
CD21	Bu32	Biolegend	Yb176

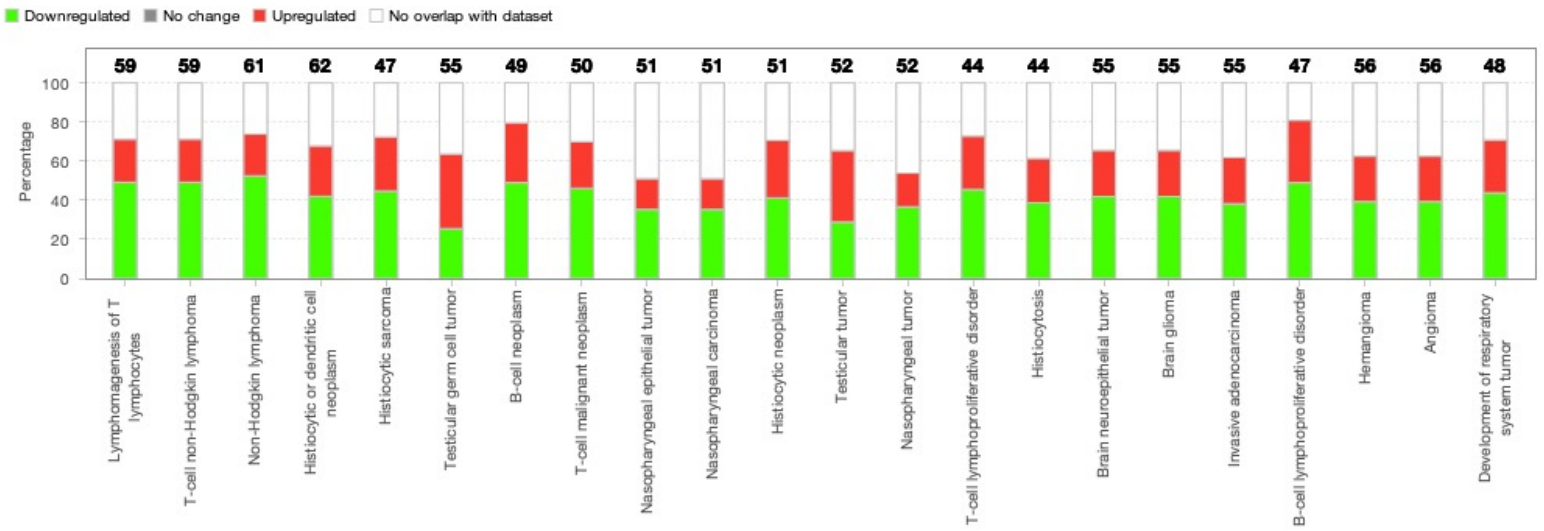
Supplementary Table 1: Antibodies used for CyTOF Mass Cytometry

	Molecules in Network	Score	Focus Molecules	Top Diseases and Functions
1	ARF5,ATXN10,CHD4,CLEC11A,CTBP1,DDRGK1,DHX9,EIF3A,EIF3B,EIF3H,FAM3C,HNRNPA1,HNRNPU,KCTD17,KRT10,LARP7,MDM2,MRN,NAA38,NTHL1,POP4,PPIA,PPIB,PRDX4,PRPF8,Rac,RPL5,RPS11,RPS13,RPS15,RPS4X,SFPQ,SSB,TKT,TPGS1	50	33	[Infectious Diseases, Organismal Injury and Abnormalities, RNA Post-Transcriptional Modification]
2	47S pre-rRNA:SSU processome,AATF,AFF3,AKAP,AKAP12,AKAP17A,BMS1,C7orf50,CAPNS1,CCDC85B,DDX10,DDX24,DDX54,DRG1,ERP29,GTPBP4,HMG20B,IFRD2,LRRCC1,LYAR,NOP53,NOP56,p85 (pik3r),RPF1,RPL35,RPL8,RPS14,RPS8,RSL1D1,SRP14,SRP72,SSU Processome,TTF1,WDR46,ZNF207	45	31	[Cell Cycle, Cell-To-Cell Signaling and Interaction, Connective Tissue Disorders]
3	AHCYL1,ATP5MJ,CAMK2,CORO1A,cytochrome C,DUT,EEF1B2,EEF1D,FDX1,GCAT,HSD17B10,HSPD1,ITM2B,ITPR,LAMTOR5,MAP1B,Mpt pore,MT-CO1,MTCH2,NOPCHAP1,NUDCD2,OAT,PHGDH,PPIF,RRAGD,SARS1,SLC25A5,SLC25A6,TIMM10,TOMM40,TRABD,UXS1,VARS1,VDAC2,VDAC3	45	31	[Connective Tissue Disorders, Developmental Disorder, Neurological Disease]
4	ATG101,ATP5F1A,ATP5F1D,ATP5PB,ATP5PD,ATP5PF,ATPAF1,BAD,COX6C,COX8A,Creb,CYC1,DDX39A,FADS3,HSP90:ATP:STIP1:HSP70:nascent protein,HSP90:STIP1:HSP70:nascent protein,HSP90AB1,HSPA8:LAMP2a multimers,HSPA9,LSM3,NDUFA1,NDUFA12,NDUFAB1,NDUFB2,NDUFB4,NDUFB6,NTAN1,PRKAA,PSMC5,SDHAF1,SH3BGRL3,SOD1,TCL1A,TRPT1,TUFM	43	30	[Neurological Disease, Organismal Injury and Abnormalities, Skeletal and Muscular Disorders]
5	28S ribosomal subunit,28S ribosomal subunit:MTIF3,39S ribosomal subunit,55S ribosome:mRNA:fMet-tRNA,55S ribosome:mRNA:tRNA:MRRF,CHCHD1,COPZ1,GPATCH4,JAK1/2,LCP1,MRPL12,MRPL13,MRPL14,MRPL21,MRPL23,MRPL27,MRPL3,MRPL32,MRPL36,MRPL37,MRPL41,MRPL42,MRPL54,MRPL55,MRPS12,MRPS15,MRPS18C,MRPS36,OXA1L,PTK2B,SPATS2,SSBP2,TMED2,TMED3,TMED9	40	29	[Cell Death and Survival, Cell-mediated Immune Response, Cellular Movement]
6	ADSL,ANP32E,ATAC B,capped, methylated pre-mRNP:CBC,CIRBP,EDF1,EFTUD2,GMDS,HNRNPDL,HNRNPR,KDELR2,LUC7L3,MAT2A,MLLT11,NOSIP,NTPCR,NXF1,2:NXT1::polyadenylated, capped mRNA:CBC:EJC:TREX:SRSF proteins,PAICS,PCBP2,PHB1,polyadenylated, capped mRNA:CBC:EJC:TREX:SRSF proteins,RAB18,RBM10,RBM3,SLC25A1,SNRPB,SON,spliced mRNA:EJC:CBC complex:Alternative splicing factor,Spliced mRNP,SRSF11,SRSF7,TRA2B,TYMS,ZC3H15,ZMAT2	40	29	[Nucleic Acid Metabolism, RNA Post-Transcriptional Modification, Small Molecule Biochemistry]
7	CLEC2B,DHRS7,EMC10,ERGIC2,FAM216A,GGH,LMAN1,LRPAP1,Mek,MFNG,MIEN1,NPC:NXF1,2:NXT1:EJC:CBC:mRNA,nucleoporin-associated Rev:Importin-beta:B23,NUP210,PXDN,RAB10,RAB11A,RAB9A,RHOBTB3,RHOBTB3:ATP:RHOBTB3 interacting proteins,RTN3,RTN4,SDF2L1,SEC61B,SEC62,SPC25,STARD3NL,STIM2,STK32C,SYVN1,TEX264,TMEM230,Ube2-ubiquitin,UBE2J1,Ubiquitin:E2 conjugating enzymes	40	29	[Cellular Assembly and Organization, Cellular Function and Maintenance, Tissue Development]
8	Ap1 gamma,ARPP21,CBX5,Cd1,CD81,CDK1/2,CFLAR:LUBAC:Ub:UBE2D3,DDX18,E2F4,EBNA1BP2,FBL,GBP4,GNL3,HNRNPK,MRPL47,NCL,NPM1,POLR1G,RBCK1,RPL17,RPL22,RPL23A,RPL30,RPL38,RPL4,RPL6,RPL9,RPLP0,RPSA,RRS1,SRSF5,TCR,TH2 Cytokine,YBX1,YBX3	40	29	[Cancer, Cell Death and Survival, Organismal Injury and Abnormalities]
9	ACAA2,ACAT1,ACAT2,acetyl-CoA C-acetyltransferase,APOO,C1QBP,CHCHD10,COX14,Cpla2,CXXC5,ECHS1,growth factor,growth factor receptor,IKK (complex),MCUB,MCUR1,MIX23,MRPL11,MRPS26,MRPS7,MTFMT,MTIF3,NDUFA5,NDUFA9,NDUFS3,NDUFV2,NME4,Pdgfr,PRDX3,PYCR2,SHMT2,Tnf (family),TRMT10C,WIPI1,YME1L1	38	28	[Hereditary Disorder, Metabolic Disease, Organismal Injury and Abnormalities]
10	BMI1,BRCA1,CYFIP1,DDIT4,DNMT1,EZH2,GOPC,H2AX,Histone h2a,HK2,HNRNPC,HSF1:HSP90:HDAC6:VCP:PTGES3,IDH2,KPNB1,LCMT1,LDHA,MACROH2A1,MIR101,NOLC1,PARP,PKM,RIF1,SARAF,SNHG7,SNRPD3,TRIM28,Ub-CDC25A,Ub-misfolded nascent CFTR:ERAD,UBC,UQCRC2,VCP,VCP:Misfolded Proteins:HDAC6:HSP90:HSF1,YY1,ZFAS1,ZNF581	38	28	[Cell Cycle, Cell Death and Survival, Organismal Injury and Abnormalities]
11	ACTB,actin/tubulin-bound CCT/TRiC:ADP,BCL11A,BUD31,C12orf57,CASK,CCDC25,CENPF,CFDP1,CPNE1,CTNNAL1,DPY30,GABP,H2BC8,HSP90:ATP:FKBP4:PTGES3:NR3C1,HSP90:ATP:PTGES3:FKBP52:NR3C1:NR3C1 ligands,INO80 alt,IRF2BP2,KIF5B,MCRS1,MET channel:Tip link:USH1C:USH1G:MYO7A:cytoskeleton (IHC),MET channel:Tip link:USH1C:USH1G:MYO7A:cytoskeleton (OHC),NBEAL1,NR3C1,OAZ1,PCBD1,PRCC,SHKBP1,SMARCE1,SRI,SS18L2,TMIE,UCHL5:INO80,UHRF1,VPS35	36	27	[Cell Cycle, Cell Morphology, Cellular Development]
12	ABHD17A,AIMP2,AK2,ASMTL,Basal body:transition zone proteins,BBS/CCT,CCT/TRiC:ADP:non-native tubulin,CCT/TRiC:ATP:unfolded tubulin,CCT2,CCT5,CCT6A,CRMP2-KLC1-Tubulin,DCTN3,DYNC1H1,DYNLL1,ENDOV,GFOD1,LY86,MAP2K1/2,MAPRE1,Misfolded Proteins:HDAC6:Dynein,NUDC,PCM1,PDCL:Partially folded G-protein beta subunit:CCT/TRiC:ADP,PSMA3,STK24,TEDC2,TRMT6,TUBA1A,TUBA1C,TUBB,TUBB2A,TUBB4B,TUBG1,Tubulin alpha/beta	34	26	[Cancer, Ophthalmic Disease, Organismal Injury and Abnormalities]
13	60S ribosomal subunit,APC (complex),ATF4:CEBPB,CEBPG,DDIT3:TRIB3 gene,BOP1,CCNG1,Eif2,ENY2,FKBP11,Mapk,MAZ,MLX,PDCD10,PFK,PHACTR1,PHACTR3,PP1 protein complex group,pyruvate kinase,RIDA,RPL14,RPL21,RPL22L1,RPL24,RPL26,RPL26L1,RPL27,RPL27A,RPL29,RPL36,RPL36A,RPL37,RPL39L,RPLP2,TRIB3,YAP/TAZ,YAP/TAZ-14-3-3	32	25	[Endocrine System Disorders, Metabolic Disease, RNA Post-Transcriptional Modification]
14	370 kDa subcomplex,AKT1,ALKBH7,ATP5,COX5B,COX7B,Cytochrome bc1,Cytochrome c oxidase core,Cytochrome c oxidase:CO,cytochrome-c oxidase,GC-GCR dimer,GLRX2,ISCU,Mitochondrial complex 1,Mitochondrial Electron Transport Chain,MT-CO3,MT-CYB,MT-ND1,MT-ND2,MT-ND3,MT-ND4L,MT-ND5,MT-ND6,NADH dehydrogenase,NDUFA8,NDUFB10,NDUFB5,NDUFC2,NDUFS4,NDUFS5,Oxphos,REX1BD,TMEM126B,UQCR11,UQCRH	30	24	[Cell Signaling, Post-Translational Modification, Protein Synthesis]
15	AKR1A1,Aldose Reductase,ARL1,ATF7IP2,C1orf21,C4orf3,CCAN:DNA:CASC5,CCAN:DNA:CASC5:Mis18,CD53,CENPM,CENPN,CISD1,CISD2,DCXR,DECR2,Eotaxin,glutathione peroxidase,glutathione transferase,GST (complex),GSTK1,GSTO1,H2AC12,ITGB1,Kinetochore:Mad1:MAD2,MGST3,NME3,PEX5S,L:Cargo protein,PEX5S,L:Cargo:PEX13:PEX14:PEX2:PEX10:PEX12,PLD4,QSOX2,SAR1A,SSR3,SSR4,Translocon:TRAP,TRAPPC2L	30	24	[Carbohydrate Metabolism, Small Molecule Biochemistry, Vitamin and Mineral Metabolism]
16	CHCHD2,CLK3,DDX17,DDX21,DDX5,DMAC1,EWSR1,GNL3:EBNA1BP2:DDX21:PES1,GUK1,HDL-cholesterol,HNRNPD,HNRNPM,InlB:MonoUb-K,MET dimer:GRB2-1:CBL:CIN85:endophilin,InlB:MonoUb-K,MET:GRB2-1:CBL:CIN85:endophilin:EPS15:HGS:STAM,INTS11,MDK,Microprocessor,PCOLCE2,PDGFRA,Pmca,PNN,PPIase:nsp1,PPIG,RNA polymerase II (2,7):RPAP2:Integrator:LEC:capped pre-snRNA:Initiation factors:snRNA gene,RNA polymerase II (2,7):RPAP2:Integrator:LEC:Initiation factors:snRNA gene,SF3B2,Sfk,SH3KBP1,SNRNP70,SRRT,THRAP3,TRA2A,VLDLR,ZCCHC17	30	24	[Cancer, Organismal Injury and Abnormalities, RNA Post-Transcriptional Modification]
17	18SE pre-40S particle,40S Ribosome-eIF3-mRNA-eIF4A-eIF4B-eIF4E-eIF4G,43S Translation Preinitiation,48s,ACAA1,ACAC,amylase,COX20,ECI1,eIF,EIF1,EIF1AY,EIF3,EIF3D,EIF3K,EIF3M,EIF4F,EIF5,Insulin,MPC2,NCBP2AS2,OXLD1,PABP,PDZD11,PHYH,RENBP,Ribosomal 40s subunit,RPP40,RPS21,RPS25,RPS27L,RPS28,RPS29,RPS4Y1,UQCC2	28	23	[Cancer, Gene Expression, Protein Synthesis]
18	AGAP1,Alpha tubulin,ARL2,ATXN2L,BDH2,CCT/TRiC:ADP,CCT/TRiC:ADP:actin,CCT/TRiC:ADP:Sphingosine kinase 1,CCT/TRiC:ATP:actin,CCT4,CCT7,CLINT1,CUTC,CYSTM1,DAAM1,EID1,GNB5:CCT/TRiC:ADP,HDDC3,MCRIP2,NAV1,PDCL3,PDCL:Partially folded G-protein beta 1-4:CCT/TRiC:ADP,PDCL:Partially folded GNB5:CCT/TRiC:ADP,peroxidase (miscellaneous),PFDN5,PRRC2A,RGS7,RGS9,(RGS6,RGS11):GNB5:CCT/TRiC:ADP,RHOA,SMAP1,SMAP2,TMEM167A,Unfolded G-protein beta subunit:CCT/TRiC:ADP,Unfolded G-protein beta subunit:CCT/TRiC:ATP,VBP1,YTHDF2	28	23	[Cellular Movement, Post-Translational Modification, Protein Folding]
19	3' end cleaved, ligated exon containing,AIMP1,APRT,AUF1 Complexed with Translation and Heat Shock Proteins,BRF1:mRNA Degradation,EGLN,EIF2AK1,EIF4G1,ELF2,EXOSC10:C1D:MPHOSPH6:SKIV2L2:Exosome,EXOSC4,EXOSC5,EXOSC9,exosome,Exosome core,Exosome:SKI,IARS1,KSRP:mRNA Degradation,LTV1,MTORC1,NOB1,PAIP2,PSMC3,RAB4A,Rab5,RBM8A,RHEB,RPS16,RPS20,RPS27,Spliced mRNA:CBC:EJC:TREX,SUMO2,THOP1,TOP2B,TTP:mRNA Degradation	26	22	[Infectious Diseases, Organismal Injury and Abnormalities, RNA Post-Transcriptional Modification]
20	B-WICH:rDNA Promoter:KAT2B:KAT2A:EP300,B-WICH:rDNA Promoter:SL1:RNA Pol I,BAZ1B,Calcineurin A,Ck2,Glycogen synthase,Gsk3,H1-3,H1-5,Histone H1,HMGN2,HMGN3,HP1,ITPA,NT5C,NUCKS1,nucleoside-triphosphate diphosphatase,Nucleosome core,NUDT14,NUDT15,NUDT5,PDAP1,Pdgf (complex),peptidylprolyl isomerase,phosphatase,PPP2R3B,PTP4A1,PTPN6,PTPN7,RPS19BP1,SET,SHP,UTP23,WDR83OS,ZBED1	24	21	[DNA Replication, Recombination, and Repair, Nucleic Acid Metabolism, Small Molecule Biochemistry]
21	Ap2,Ap2 alpha,BCR (IgM class),CCDC167,CD164,CD19,CD22,CD79A,CD79B,CSF,DPM3,FAM177A1,GTPBP6,IgD,Immunoglobulin,LEPROTL1,MFSD12,RRP15,SELENOS,SERP1,SUSD3,Tail-anchored protein:ASNA1:ADP,Tail-anchored protein:ASNA1:ADP:WRB:CAMLG,Tail-anchored protein:ASNA1:ATP,Tail-anchored protein:SGTA dimer,Tail-anchored protein:SGTA:BAG6:GET4:UBL4A:ASNA1:ATP,TGS1,TMEM129:DERL1:VIMP:VCP:Ub:UBE2J2, TMEM129:DERL1:VIMP:VCP:UBE2J2,TMEM147,TMEM14B,Ub:UBE2J2,UBE2J2,US11:HLA:TMEM129:DERL1:VIMP:VCP:Ub:UBE2J2,ZDHHC24	23	20	[Cancer, Hematological Disease, Immunological Disease]
22	AASDHPPT,ANKRD39,ARL6IP6,CKS1B,Cyclin E/A:CDK2:CDKN1A,CDKN1B:CUL1:SKP1:SKP2:CKS1B:3xubiquitin,cytokine,DDB1/DDB2/CUL4A/RBX1,DDB2,Fcgr3,GG-NER incision complex:Open bubble dsDNA,GG-NER pre-incision complex:Open bubble-dsDNA,GPN1,GPN3,GYG1,H2AZ2,MAC,Open bubble-dsDNA:PAR-UV-DDB:TFIIH Core:XPA:PAR-PARP1, PAR-PARP2:CHD1L,OSTC,PFDN2,PHPT1,PITHD1,PKMYT1,Prefoldin-associated actin/tubulin,RNASEH2C,RPS6KA,SNX3,SPINT2,TMEM183A,Ub:XPC:RAD23:CETN2:Distorted dsDNA:UV-DDB,Ub:XPC:RAD23:CETN2:Distorted dsDNA:UV-DDB:PARP1,PARP2,UV-DDB:COP9 Signalosome,UXT,WDR54,XPC:RAD23:CETN2:Distorted dsDNA:UV-DDB	23	20	[Cell Cycle, Cell Morphology, Reproductive System Development and Function]
23	CDC40,CTNNBL1,Deadenylated mRNA:Lsm1-7,GINS2,IFITM2,Interferon alpha,ISGF3 bound to ISRE promotor elements,LSM12,LSM2,LSM2-8,LSM4,LSM5,LSM6,LSM7,LY6E,PQBP1,PRP19-CDC5L,PRPF38A,RBMX2,snRNP,snRNP-IgG Immune complex,SNRNP25,SNRPB2,SNRPC,Spliceosomal B Reactome,Spliceosome B,Spliceosome B activated,Spliceosome B star,Spliceosome C,Spliceosome C star,Spliceosome P,SRRM1,U1 snRNP,WBP4,ZNF511	23	20	[Cell-To-Cell Signaling and Interaction, RNA Damage and Repair, RNA Post-Transcriptional Modification]
24	26s Proteasome,ADRB,BIRC5,CASP4,CDK6,CEBPB,Dynamin,E2F1,E2F1:TFDP1,TFDP2:RRM2 gene,EZH2 Gene:E2F1/2/3:DP1/2,Ferritin,FTL,GSDMD,HISTONE,JTB,LHFPL6,PEX2:PEX10:PEX12:PEX5L:Ub:UBE2D1,2,3:PEX7:PEX13:PEX14,PEX2:PEX10:PEX12:PEX5S,L:Ub:UBE2D1,2,3:PEX13:PEX14,PSMC1,PSMD4,RIPK1:STUB1:Ub:UBE2D3,RNF181:BCL10:Ub:E2,SMC1A,SMC3,SOX4,Stat3-Stat3,Synaptonemal,TCF4,Ub:UBE2D1,UBE2D2,UBE2D3, UBE2E1,UBE2N,Ub:UBE2D3,UBE2D1,2,3:Ubiquitin,UBE2D3,UBE2I,Ubiquitin,VPS28	19	18	[Cellular Development, Cellular Growth and Proliferation, Organismal Survival]
25	ADP:Calcium Bound Sarcomere Protein,ALDH3A2,AP3D1,ATP:Calcium Bound Sarcomere Protein,Calcium Bound Sarcomere Protein,CLTC,DYRK4,EFHD2,EGF-like ligands:EGFR:CBL:Ub-Y53/55-SPRY1/2,EGF-like ligands:Ub-EGFR:CBL,EGF-like ligands:Ub-EGFR:CBL:GRB2,FGFR1,FSH,GPIIB-IIIA,HAX1,HBEGF,HSPA8,Inactive Sarcomere Protein,Laminin (complex),LAMP1,MAP1LC3B,MYH9,P110,PLC gamma,PTK,RAB13,RAB5C,RAC2,Rsk,SLC3A2,STUB1,SYK/ZAP,TTN,Ub-Activated FGFR1 complex:Ub-FRS2,VAV	19	18	[Cell Morphology, Cellular Assembly and Organization, Cellular Function and Maintenance]

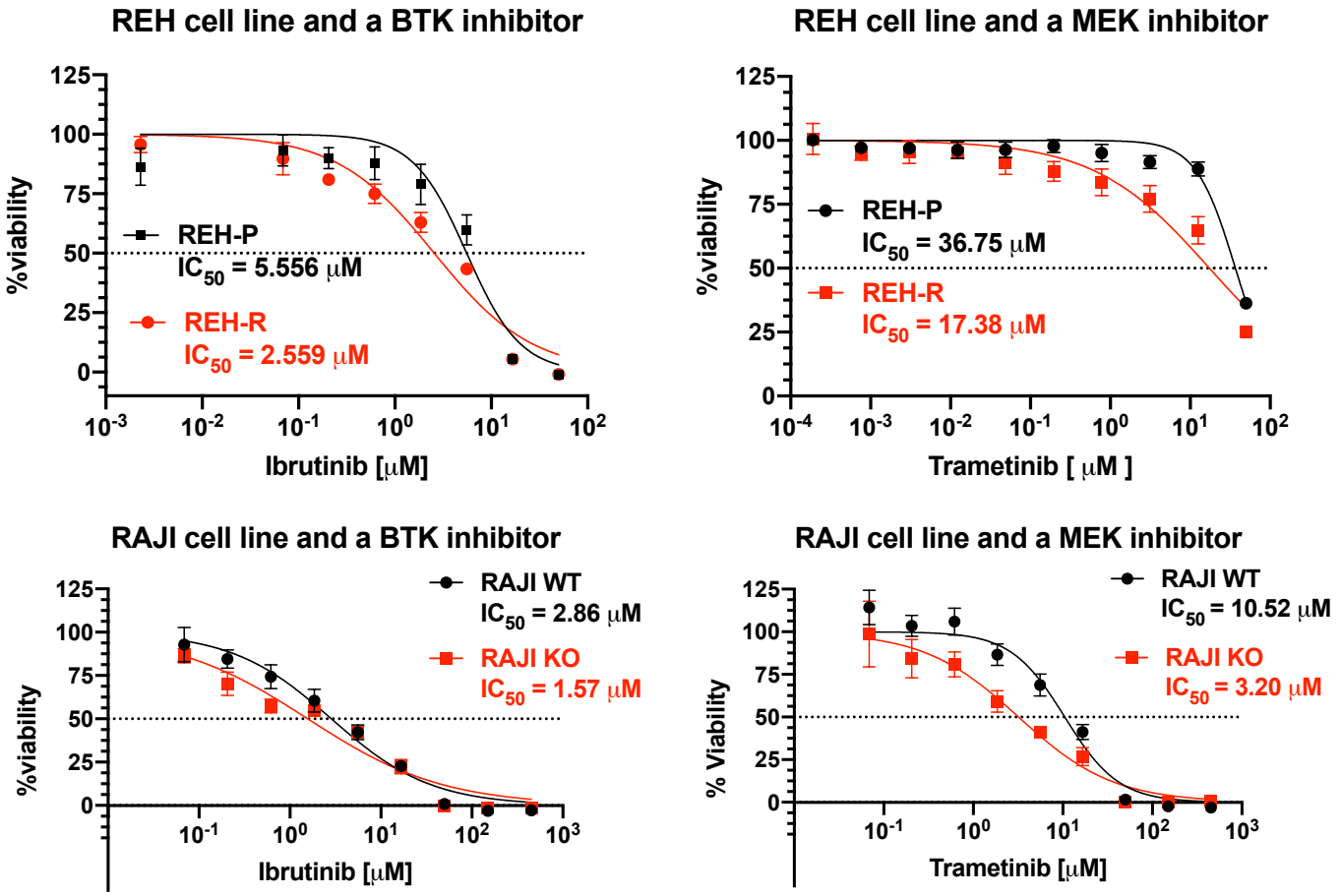
Supplementary Table 2: Ingenuity pathway analysis on N6 scRNAseq showing networks with significant expression changes in N6 parental vs resistant analysis.

	Molecules in Network	Score	Focus Molecules	Top Diseases and Functions
1	AIG1,ASGR2,C11orf96,C4orf45,CCDC125,CPNE7,CYBRD1,EBF3,FA2H,FLYWCH1,FXYD6-FXYD2,KIF6,LRRC17,LRRC3B,MLLT10,NFATC1,OTOS,PARVG,PRDM15,SLC16A13,SLC34A2,SPNS3,SS18,SYNDIG1,THAP4,TMCO5A,TMEM120A,TMEM160,TMEM178A,TMEM60,TSPAN18,TTC32,ZNF219,ZNF423,ZNF521	37	35	[Cancer, Endocrine System Disorders, Gastrointestinal Disease]
2	BMI1,CAND1,CAPZB,CLUH,CNTN4,CTSD,DEF6,DPYSL2,ENOX1,HHLA1,HOMER1,INO80D,KIF23,KPNB1,LAMB4,MATR3,MYBBP1A,NHLRC2,PFKM,PLEC,PRPF40A,RCC2,RRBP1,RUVBL1,SERBP1,SPDL1,STAU1,SYNE3,TUBB4A,UFL1,WWP2,YBX3,ZKSCAN1,ZNF385B,ZNF597	37	35	[Cancer, Gastrointestinal Disease, Organismal Injury and Abnormalities]
3	ADAMTSL3,C17orf50,C6orf15,CARHSP1,CCDC33,CD300LG,CELF5,DMRT3,DOP1B,FAM118A,GLRX3,IGFN1,Integrinα,ITGA9,ITGAM,ITGB1BP1,KHDC1,KRTAP13-1,KRTAP5-7,NBPF10 (includes others),NOTCH2NLA/NOTCH2NLB,OLIG3,OXER1,PCED1B,PCSK5,PROP1,S100PBP,SLC43A2,SMOC1,STAC,STK16,TBX22,TRIM42,VGLL3,ZFY	34	34	[Cell-To-Cell Signaling and Interaction, Connective Tissue Development and Function, Connective Tissue Disorders]
4	ABL1,AKAP1,BCAT2,CAST,CPEB3,cytochrome C,DNAH7,GPD2,GTF2IRD1,HK1,KASH5,LRRC49,LRRC66,MEGF11,MST1R,MTX2,NAALADL1,PPFIBP1,RAB11A,RAB5C,RAB7A,RTN4,SCAMP1,SEC23IP,SHANK3,SLC25A51,SLC30A9,SLC9A7,STOM,SYNE1,TMEM43,TXN2,VDAC1,VPS33A,ZCCHC2	34	34	[Cancer, Organismal Injury and Abnormalities, Reproductive System Disease]
5	ADARB2,CABYR,CEP112,ERCC6L2,FAM166B,FAM168B,FHL5,FSTL4,GIGYF2,GPATCH2L,Inpp5,INPP5D,INPP5E,LETM2,MAP7D2,MELK,MISP,MORN3,MYOZ3,NEAT1,NEK6,Opsin,PLEKHA5,PNMA2,PPM1H,ROPN1,RTP5,SALL3,SH3PXD2A,STARD13,TEX19,ZCCHC7,ZNF438,ZNF648,ZNF766	32	33	[Carbohydrate Metabolism, Lipid Metabolism, Small Molecule Biochemistry]
6	AMBP,ARRDC3,BRINP2,CMTR1,CSMD1,CUEDC1,DLGAP4,GZMK,Iti,ITIH2,ITIH5,KCNK9,KIF16B,KIF3C,LCN,LCN8,LDLRAD4,MON2,MPP7,NCAPG2,NPLOC4,OBP2B,ORM2,PRSS8,RFFL,SEZ6L,SPIN1,SPINT2,SV2C,SZRD1,TM4SF4,TMEM168,TNFSF13B,TRIM66,TRMT6	32	33	[Carbohydrate Metabolism, Developmental Disorder, Small Molecule Biochemistry]
7	ANKRD11,CERS2,KRAB-ZNF / KAP,ROCK1,SETX,TRIM54,TSG101,VAV,ZFHX3,ZFP69,ZNF100,ZNF155,ZNF175,ZNF230,ZNF287,ZNF33B,ZNF41,ZNF433,ZNF443,ZNF485,ZNF492/ZNF98,ZNF554,ZNF557,ZNF596,ZNF599,ZNF615,ZNF671,ZNF709,ZNF713,ZNF716,ZNF717,ZNF718,ZNF750,ZNF791,ZNF860	32	33	[Cancer, Organismal Injury and Abnormalities, Respiratory Disease]
8	ANXA2,AP3D1,BICD1,CASP1,CCSAP,CDK6,DIPK1C,DYNC1LI1,FGFR4,GFI1,GSDMC,HORMAD2-AS1,Hsp90 (family),HSPA9,INTS1,IRAK1,KIT,MAP4K3,MOXD1,NEDD9,NTRK1,PAK2,RANBP9,SH3KBP1,SYNPO2,TANK,TAX1BP1,TNFRSF8,TNIP2,TNK2,TRAF3IP2,TRAF4,TRAF5,Ubiquitin,ZNF823	32	33	[Cancer, Organismal Injury and Abnormalities, Respiratory Disease]
9	BAIAP2,BAIAP2L1,C6orf132,CAMLG,CEMIP2,EVL,FAM91A1,FHIP2A,FLNC,GAPVD1,HLCS,IRF4,ISGF3 bound to ISRE promotor elements,KIAA1522,LHFPL4,LNPK,NUDT16,PRDM10,PTP4A1,PTP4A2,RAB35,RAP1GDS1,RASL11B,SEC63,SLC25A46,SNX24,SNX29,STBD1,TACC1,TACC2,Tail-anchored protein:ASNA1:ADP:WRB:CAMLG,TEX2,TMSB4,TNFAIP8,TSSK1B	30	32	[Cancer, Cell Cycle, Cell-To-Cell Signaling and Interaction]
10	ANKFY1,AP3M1,CAPN13,CCDC88A,CEP19,CTNNA1,DCAF8L2,DLG5,DNAAF10,JMY,KIF11,KPNA4,KSR2,MARK2,MTCL1,NAA11,NS1 homodimer:Importin,PARD3,PDRG1,PHLPP1,PLD1,PPHLN1,PPP6R3,RASSF10,RBM26,REV1,SFSWAP,TJP2,TNKS1BP1,TP53BP2,VE-cadherin-Catenin,YAP/TAZ,ZC3H15,ZC3H4,ZYG11B	30	32	[Cell Death and Survival, Infectious Diseases, Organismal Injury and Abnormalities]
11	BGLAP,BMAL1,CNBP,DDX27,DIO2,FCHO1,GPAM,Ifn gamma,IGHV1OR15-1,KLF15,KLF8,LARP1,LARP1B,LIN28A,MAP7,MUC12,NKRF,PPARGC1B,PRDM2,PURPL,RABGAP1L,RIN3,RPL21,RPL36,RPL37A,RPL6,RPLP1,RUNX2:MAF:BGLAP gene,SNORD61,TRIM31,TUT7,VLDL-cholesterol,ZBTB24,ZNF16,ZNF44	30	32	[Embryonic Development, Organ Morphology, Organismal Development]
12	ADAMTSL2,Alpha Actinin,ARHGAP24,B3GNT2,CAPSL,carboxylic ester hydrolase,CES2,DCAF10,EML4,H2BC11,IARS1,KIF2A,LMNB2,LOXL2,LOXL4,NACA,NDST1,NEK9,PAM,PATJ,PKN2,Ras homolog,SCYL1,STOX2,TAGLN2,TECPR1,TKT,TUBB2A,TUBB8,WBP2NL,WDR1,WFIKKN1,ZNF813,ZNF836,ZNF93	30	32	[Cellular Movement, Developmental Disorder, Neurological Disease]
13	ABCB5,ACOX3,ARHGEF10L,B3GNT7,BRF2,BZW2,C3orf18,CAMTA1,COPG1,DYM,EIF2B3,GSDME,MIR124,MLYCD,MOGAT1,MTSS2,NMNAT3,NUDT19,PCGEM1,PEX14,PEX3:PEX19:class I PMP,PEX5S,L:Cargo protein,PEX5S,L:Cargo:PEX13:PEX14:PEX2:PEX10:PEX12,PPP1R15B,PTPRC,PXMP4,SKAP2,SLC27A2,SLC39A11,SNTG1,SRGAP1,SSR3,TMEM38B,TPST2,XPO6	28	31	[Lipid Metabolism, Nucleic Acid Metabolism, Small Molecule Biochemistry]
14	alpha-adrenergic receptor,ARHGAP25,C5orf24,CCT8L2,CELF1,CELF2,CFAP20,CIZ1,CKMT2,DCLK1,FAM110B,FOXN4,GATB,HERPUD1,hnRNP H,MAP2K1/2,MAT2B,MN1,MOB2,NOVA2,PKNOX1,PTBP2,RBM46,RBPMS2,RFX2,RFX3,SFT2D2,SH3BP4,SLC8A1,THUMPD2,THUMPD3,TSPYL5,UCKL1,USP30:MOM proteins,ZFAND2B	28	31	[Developmental Disorder, Hereditary Disorder, Neurological Disease]
15	AGK,ANO10,C1orf21,CACHD1,Cathepsin,CTSO,DENND2B,Dgk,DGKD,DGKK,DHRS2,DIP2B,EMP2,GFOD1,KIAA0040,KRAS,Lysosomal Protease,MEAK7,mir-3180,mir-340,MPZL1,MTRR,NAB1,ONECUT2,PLEK2,PRICKLE4,SBF1,SHISA2,SPG7,STON1-GTF2A1L,TMEM161A,USP17L,USP17L22 (includes others),VSTM5,ZNG1B	28	31	[Cell Death and Survival, Embryonic Development, Organismal Injury and Abnormalities]
16	apyrase,ATXN8OS,CCDC198,DHRS9,ELFN1,ELFN2,EMB,ERC1,ERC2,FAM9B,FCHSD2,GOLGA1,HSD17B,HSD17B1,KIAA0513,LENG1,LNX2,LZTS1,MICAL3,mir-204,mir-217,NADH2 or NADPH2 1 atom incorporation:oxygen oxidoreductase,NBAS,NCOA7,Nfat (family),PDZRN4,PHYKPL,PRKAR1B,RSRC1,TANC1,TBC1D1,TBC1D5,TEX28,TFDP3,VPS26C	28	31	[Cellular Development, Hereditary Disorder, Neurological Disease]
17	28S ribosomal subunit,28S ribosomal subunit:MTIF3,55S ribosome:mRNA:fMet-tRNA,55S ribosome:mRNA:tRNA:MRRF,AFG3L2,AK4,AURKAIP1,CCSER1,CLPX,COQ8A,ERAL1,FBXL17,GLI4,LARS2,MCAT,MRM1,MRPL33,MRPL46,MRPS27,MRPS5,MTFMT,MTHFD1L,MTIF3,NME4,PCCB,PDCD1,RTN4IP1,SLC4A11,SMIM20,TIMM21,TMEM223,TRAP1,TRMT5,ZKSCAN2,ZNF574	28	31	[Hereditary Disorder, Metabolic Disease, Organismal Injury and Abnormalities]
18	AMPD2,ARID1B,BCHE,BCL7A,BCORL1,C2orf27A/CDRT15P3,CA5A,CHD7,CHD8,CWH43,DIAPH2,ERG,ETV4,EVI5,FAM174B,GKN2,H2BC3,IL7R,KLHL4,LHX2,Osteocalcin,PCAT5,PHACTR4,RAI1,REP15,RESF1,RUNX1:CBFB:SWI/SNF,SH3TC1,SLC45A3,SMARCA2,SMARCB1,SWI/SNF chromatin remodelling,SWI/SNF chromatin remodelling complex:PRMT5:pT5-WDR77,TFCP2L1,VAX2	28	31	[Cancer, Gastrointestinal Disease, Organismal Injury and Abnormalities]
19	ACTG2,ADP:Calcium Bound Myosin Actin,ANXA11,ANXA6,ATP:Calcium Bound Myosin Actin,BRPF3,Calcium Bound Myosin Actin,CALD1,COPS7A,CST5,DCAF12,DCP2,FGGY,GPC1,GPC6,IDH3B,Inactive Myosin Actin Contractile,LGALS9,NHERF2,NSFL1C,OAT,PALS2,PDCL3,PIEZO1,PNPLA1,RORC,SLC1A3,SLC25A10,SLC25A24,SLC7A2,SORBS1,SRP9,TARS1,TOMM40,ZNF491	28	31	[Amino Acid Metabolism, Molecular Transport, Small Molecule Biochemistry]
20	CCL22,CD79A,CD79B,CHST15,CSF1R,EBF1,EBF1:LDB1:LHX2:Intergenic olfactory enhancer:Olfactory Receptor gene,HCK,IgD,IL17R,INPPL1,MKK3/6,OR1D5,OR1E1,OR1E2,OR1J2,OR1M1,OR2F1,OR4C46,OR4C5,OR4E1,OR4F17 (includes others),OR4F21 (includes others),OR5A2,OR5B21,OR6B3,OR6C4,OR6J1,OR6S1,OR6X1,OR8B8,PAX5,PHKG1,SH2B2,VPREB1	28	31	[Cell-To-Cell Signaling and Interaction, Cellular Development, Nervous System Development and Function]
21	1-acylglycerol-3-phosphate O-acyltransferase,ABHD17C,AGPAT3,amylase,AMZ1,CACNA1E,CAMKV,DCLK2,FIBCD1,GOLT1A,GPAT2,GPM6A,High voltage-activated calcium channel,JCAD,LAMP5,LCLAT1,LMBR1,LPCAT3,MAPT,MBOAT2,MEI1,Microtubule Associated,NHSL1,PHYH,RNF24,SLC22A16,STOX1,SYN2,Synapsin,TMEM104,TRIM3,TSPAN3,TSPAN5,VKORC1L1,ZFYVE28	26	30	[Cancer, Connective Tissue Disorders, Developmental Disorder]
22	ABTB2,ANKLE2,ARAP3,BNIP3,Collagen type VI,EHBP1,ERF,ESRP2,ETV3,EVC2,FNDC3A,IFT B,IFT B*,IFT57,IFT81,KIAA1671,KLHL26,NPAS1,PDXDC1,PLEKHG7,PRELID2,PTRH2,RIN1,SLC18A1,SLC18A2,SLC45A4,SMTN,SPNS2,TCF23,Tgf beta,Timp,TNS4,TRAF3IP1,TTC30B,UBXN6	26	30	[Cell-To-Cell Signaling and Interaction, Drug Metabolism, Small Molecule Biochemistry]
23	AGTRAP,ALS2,ATP10B,CADPS,CYB5A,CYB5B,FAM117B,GALNT9,HMOX1,HPCAL1,ICAM5,IQSEC1,Kcnj,KCNJ1,KCNJ15,KCNJ18,KCNJ2,KCNJ9,MIEF2,NAPA,OGDHL,PHACTR3,PRB1/PRB2,RETREG1,SEC22B,SEC61B,SLC35A3,SPIN4,STX1A,Tail-anchored protein:ASNA1:ADP,Tail-anchored protein:ASNA1:ATP,Tail-anchored protein:SGTA dimer,Tail-anchored protein:SGTA:BAG6:GET4:UBL4A:ASNA1:ATP,TPK1,UGT8	26	30	[Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization, Nervous System Development and Function]
24	2x RET:GDNF:GFRA complexes with, without SHC1:GRB2-1:GAB1,GAB2:PTPN11,47S pre-rRNA:SSU processome,ARHGEF4,BBX,CENPU,CHIC1,CLIP2,ETV6,FARP1,FGFBP1,FOXB1,GAB2,IL15:IL15RA:IL2RB:JAK1:IL2RG:JAK3:SHC1:GRB2:GAB2,KNOP1,KRR1,NAT10,NEPRO,NIFK,NOL10,NOP53,NSRP1,PARN,PIP4K2A,PPIL4,RBM28,Rnr,RPL26L1,RRP8,SNORD3A,SSU Processome,SUGP2,URB2,UTP14A,UTP25,WDR36	26	30	[Cellular Growth and Proliferation, Connective Tissue Disorders, Embryonic Development]
25	ACSL3,AHNAK,ALPP,ATP2A1,ATXN10,BRF1,CCDC47,CCDC8,CD3 group,CDK4/6,CENPV,CYB5R1,DERL1,EMC2,ENPP7,EPHX1,EPHX3,epoxide hydrolase,ERGIC1,LIG3,LTA4H,MAC,MARCHF5,NIBAN2,NIPA1,NOMO1 (includes others),PANX1,PLC gamma,POR,PYGB,RHBDD1,SDS,SLC25A26,STT3B,UBIAD1	26	30	[Cell Death and Survival, Renal and Urological System Development and Function, Renal Necrosis/Cell Death]

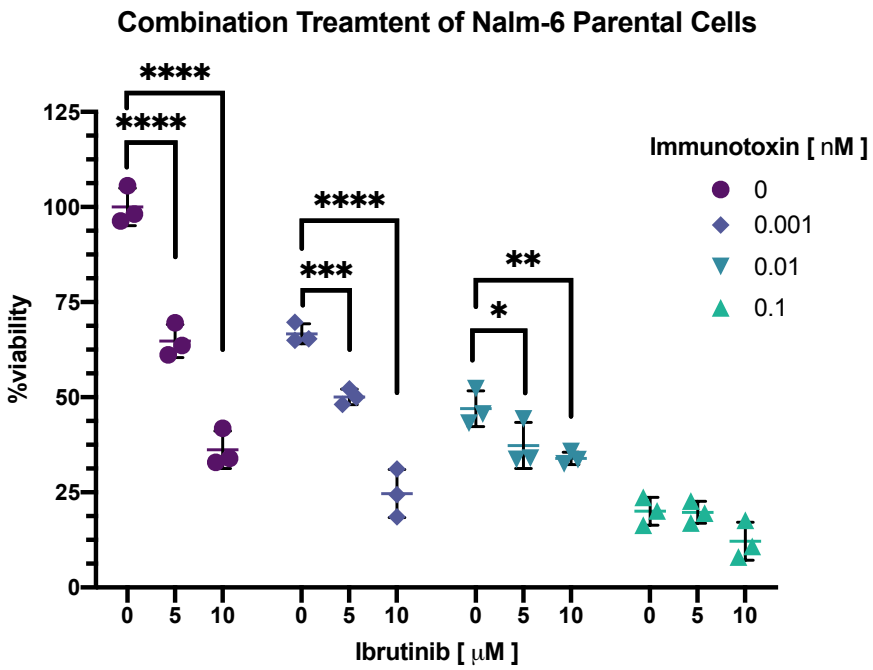
Supplementary Table 3: Ingenuity pathway analysis on REH ATACseq showing networks with significant expression changes in REH parental vs resistant analysis.



Supplementary Fig 2: Ingenuity pathway analysis on N6 scRNAseq showing up and down regulation of genes in disease pathways.



Supplementary Fig 3: Resistant REH cells (n=4) and RAJI CD19 KO cells (n=5) were more sensitive to BTK and MEK inhibition than parental and WT cells, respectively.



Supplementary Fig 4: Parental Nalm-6 cells treated with anti-CD19 immunotoxin and BTK inhibitor, ibrutinib, alone in combination show significant loss of proliferation in combination treated cells (n=3). Significance was determined using 2-way Anova.