Supplementary Information (SI) for RSC Chemical Biology.

Supplemental Tables and Figures

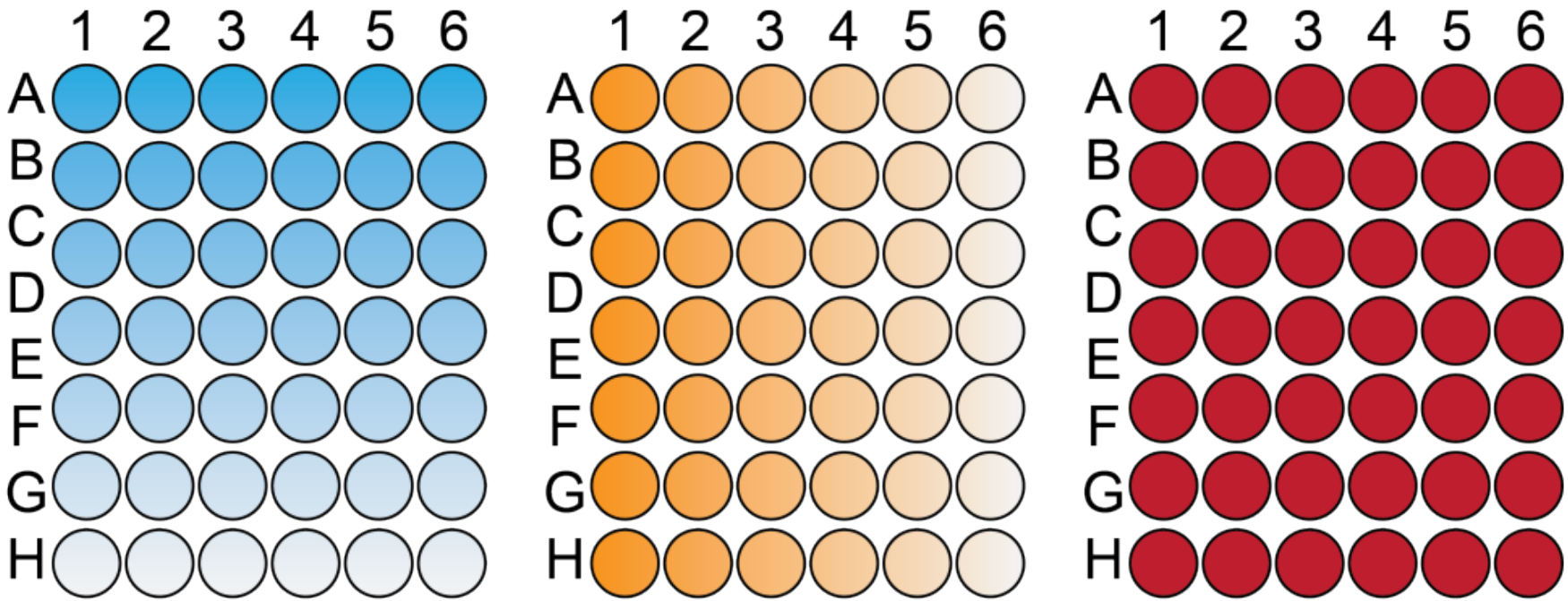
	Components
	10 g/L malt extract, 4 g/L glucose, 4 g/L yeast extract, pH 7.2
	Base media, 1.5 mM LaC_2
	Base media, 120nM rifampin
	Base media, 1% *R. wratis*
	Soluble starch 5 g/L, glucose 6 g/L, corn steep liquor 2.5 g/L proflo solid 5 g/L, proflo oil 2 mL/L, pH 7.2

Supplementary table 2. Flow cytometry reagents

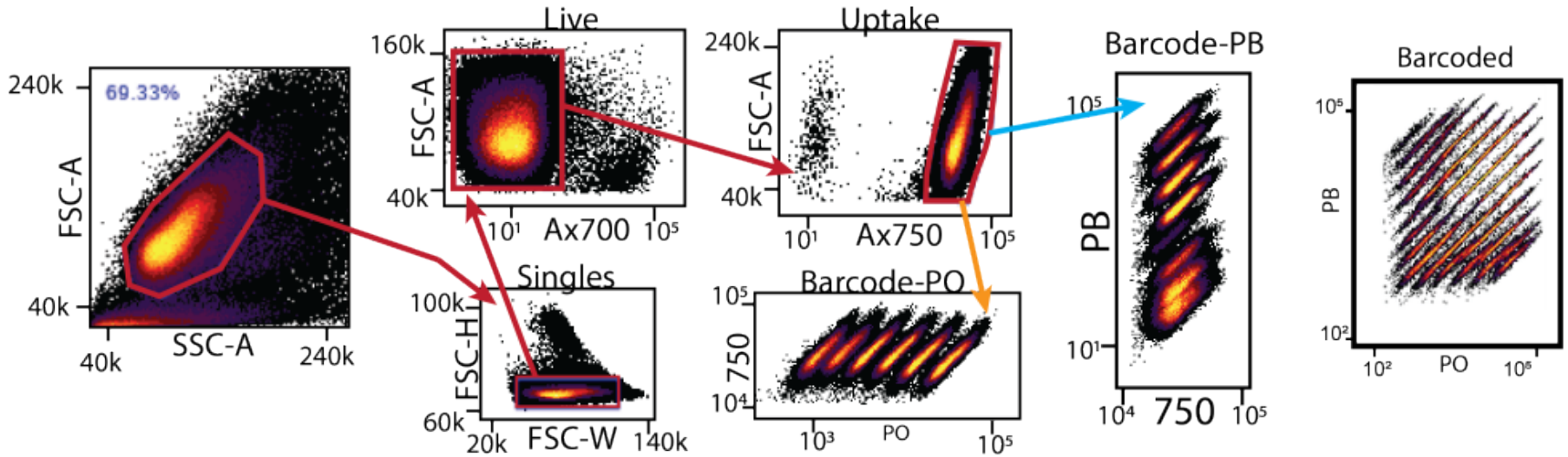
Reagent	Detect	Clone/Dye	Fluorophore	Manufacturer	Catalog number
Antibody	γH2AX	N1-431	Percp-Cy5.5	BD Biosciences	564718
Antibody	cCAS3	C92-605	PE	BD Biosciences	550822
Antibody	P-S6	D57.2.2E	Ax647	Cell Signaling Technology	4851S
Antibody	p-HH3	HTA28	Pe-Cy7	Biolegend	641011
DNA dye	Nucleic Acids	YoPro	Ax488		
NHS dye	Primary amines		Pacific Blue	ThermoFisher Scientific	P10163
NHS dye	Primary amines		Pacific Orange	ThermoFisher Scientific	P30253
NHS dye	Primary amines		Ax750	ThermoFisher Scientific	A20011
NHS dye	Primary amines		Ax700	ThermoFisher Scientific	A20010
NHS dye	Primary amines		Ax750	ThermoFisher Scientific	A20011

Genetic Information
IDH1 R132H normal cytogenetics
FLT3 ITD and 46, X, -Y, t(2;21;8)(q13;q22;q21.3), +6 [19]/46, XY [1]
IDH1 R132C and DNMT3A R882H normal cytogenetics
FLT3 D835Y and NRAS G13D and NPM1 W288C288fs*12 normal cytogenetics

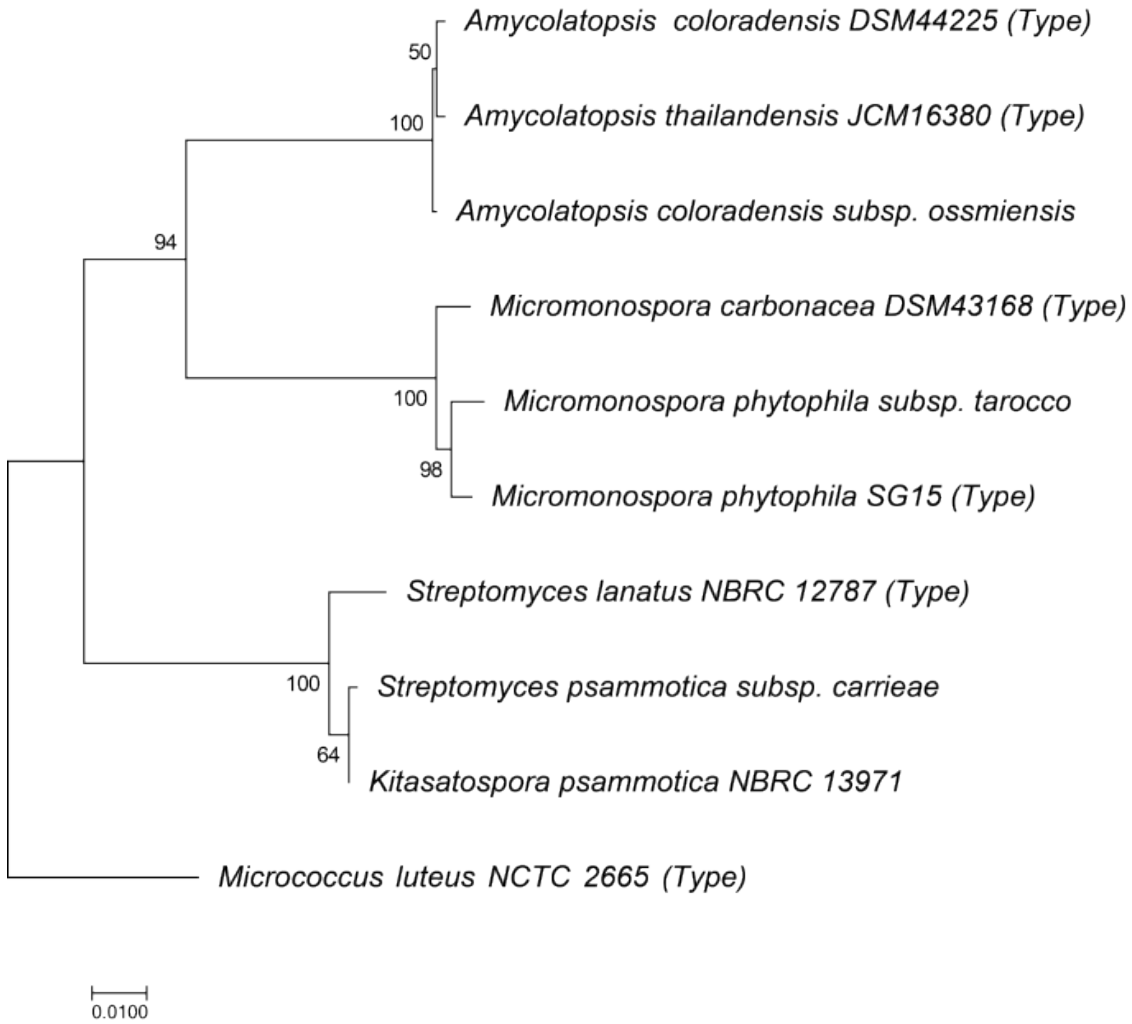
	Marker	Location	Phospho-site
89Y	CD45	Surface	
209Bi	CD11b	Surface	
175Lu	CD14	Surface	
173Yb	CD184	Surface	
170Er	HLA-DR	Surface	
169Tm	CD19	Surface	
168Eer	CD71	Surface	
165Ho	CD16	Surface	
163Dy	CD33	Surface	
162Dy	CD8a	Surface	
161Dy	CD90	Surface	
160Gd	CD13	Surface	
159Tb	CD11c	Surface	
154Sm	CD3	Surface	
151Eu	CD123	Surface	
149Sm	CD38	Surface	
148Sm	CD34	Surface	
146Nd	CD64	Surface	
145Nd	CD4	Surface	
144Nd	CD15	Surface	
143Nd	CD117	Surface	
141Pr	CD235	Surface	
193Ir	DNA	Intracellular	
191Ir	DNA	Intracellular	
176Lu	cMyc	Intracellular	
172Yb	p-S6	Intracellular	S235, 236
171Yb	Ki67	Intracellular	
167Er	p-Erk	Intracellular	Y202, 204
166Er	p-NFkB	Intracellular	p65_S529
164Dy	IkBa	Intracellular	
158Gd	p-STAT3	Intracellular	
156Gd	p-P38	Intracellular	
153Eu	p-STAT1	Intracellular	Y701
152Sm	p-AKT	Intracellular	S473



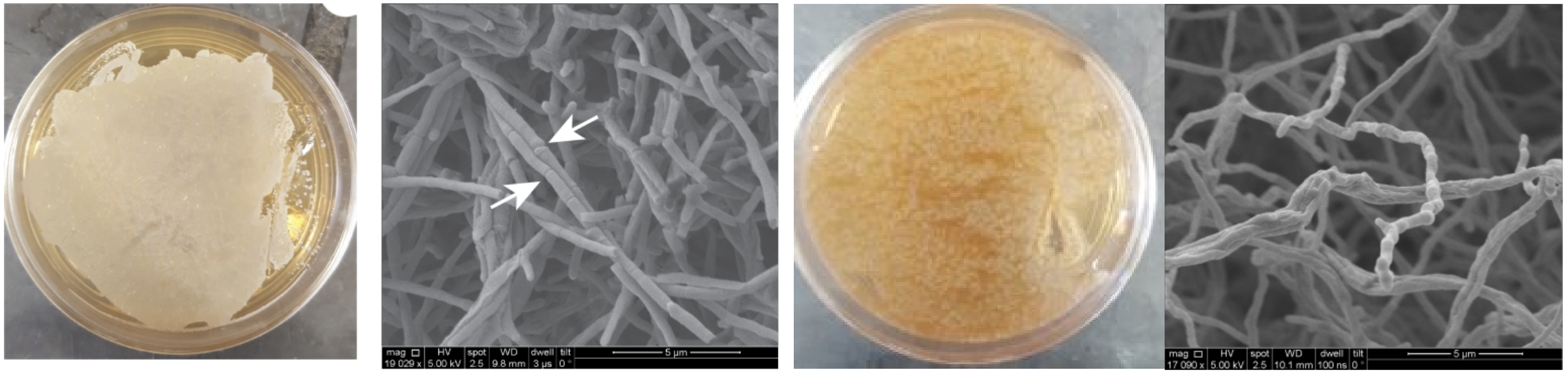
Supplemental figure 1. Cell populations are color coded by eight row-oriented levels of pacific blue (A-H) and six row-oriented levels of pacific orange (1-6). Ax750 level is consistent in all wells to control for dye uptake. Tri-color staining occurs on a single plate.



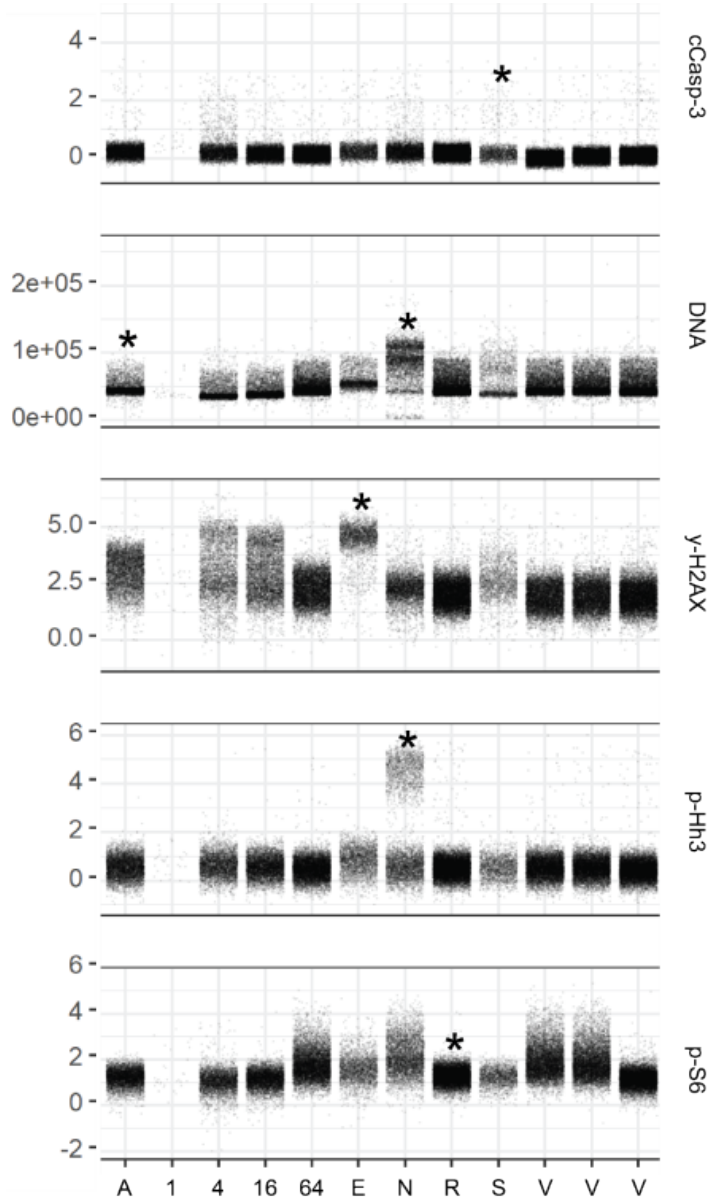
Supplemental figure 2. Approximately 500,000 fluorescently labeled cells are acquired by flow cytometry and gated for single, viable cells with conserved Ax750 dye uptake. Eight levels and six levels of pacific blue (PB) and pacific orange (PO), respectively, coordinate 48-plex barcoded experiments.



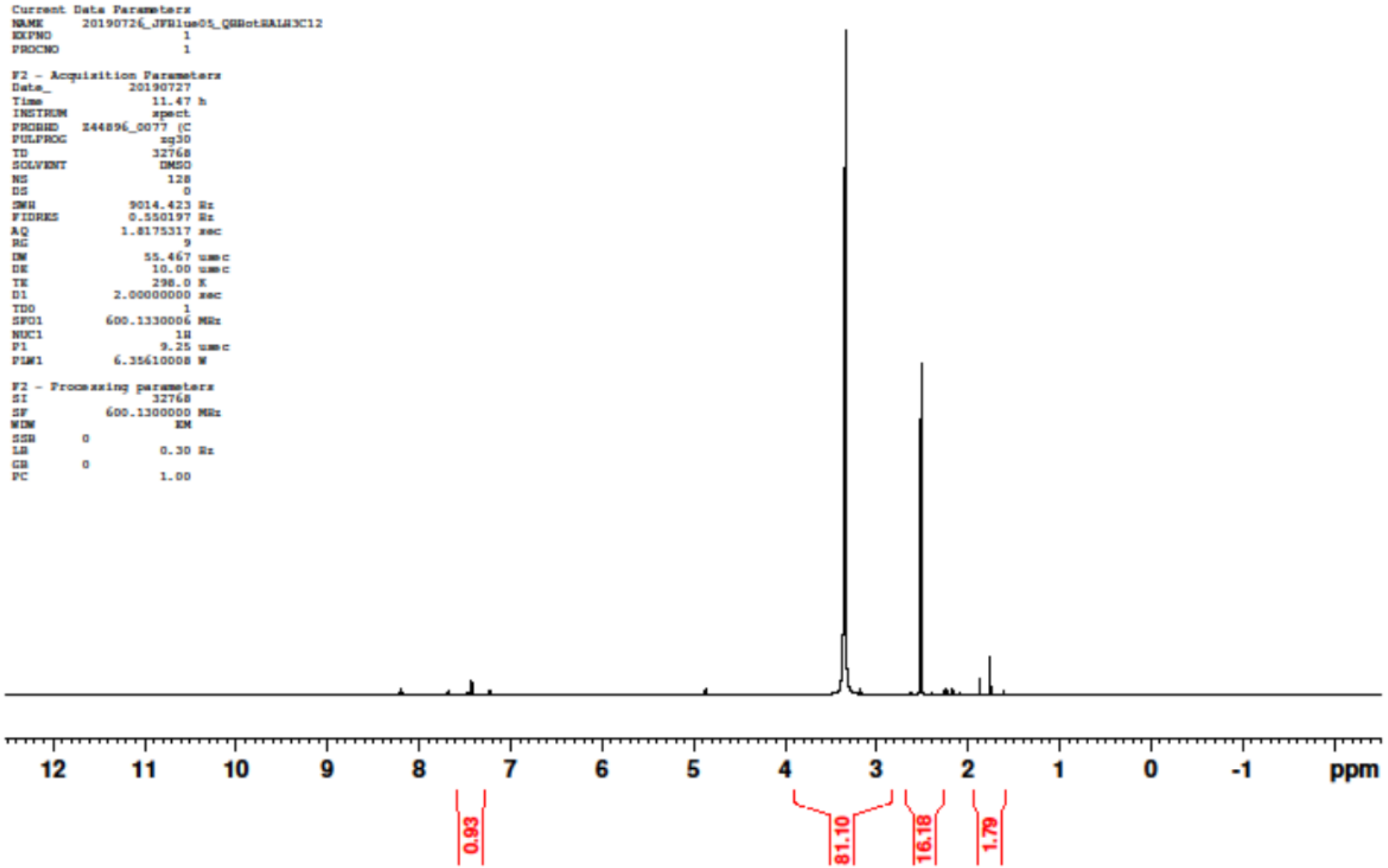
Supplemental figure 3. Phylogenetic tree of isolated bacterial strains from Blue Spring Cave (Sparta, TN) compared to type strains. The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura-Nei model [1]. The tree with the highest log likelihood (-3556.80) is shown. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 10 nucleotide sequences. All positions containing gaps and missing data were eliminated. There were a total of 1369 positions in the final dataset. Evolutionary analyses were conducted in MEGA7 [2].



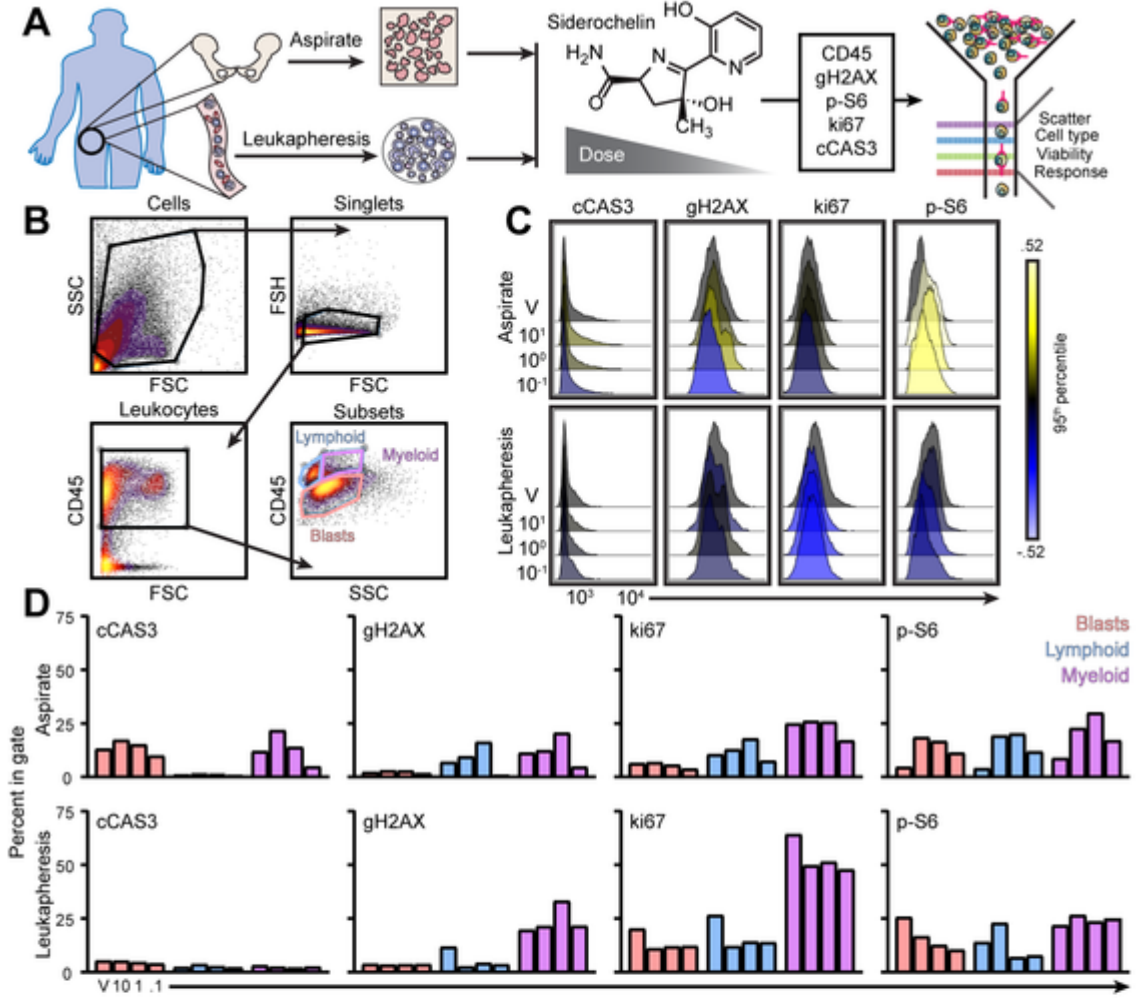
Supplemental figure 4. Left) *A. coloradensis* ssp. *ossmiensis* cultured on ISP-2 agar is white and opaque. Scanning electron microscopy reveals rod-like spores with clear segmentation. **Right)** S. Psammoticus on ISP2-agar forms white opaque puncta. SEM reveals smooth aerial mycelia with bud like projections.



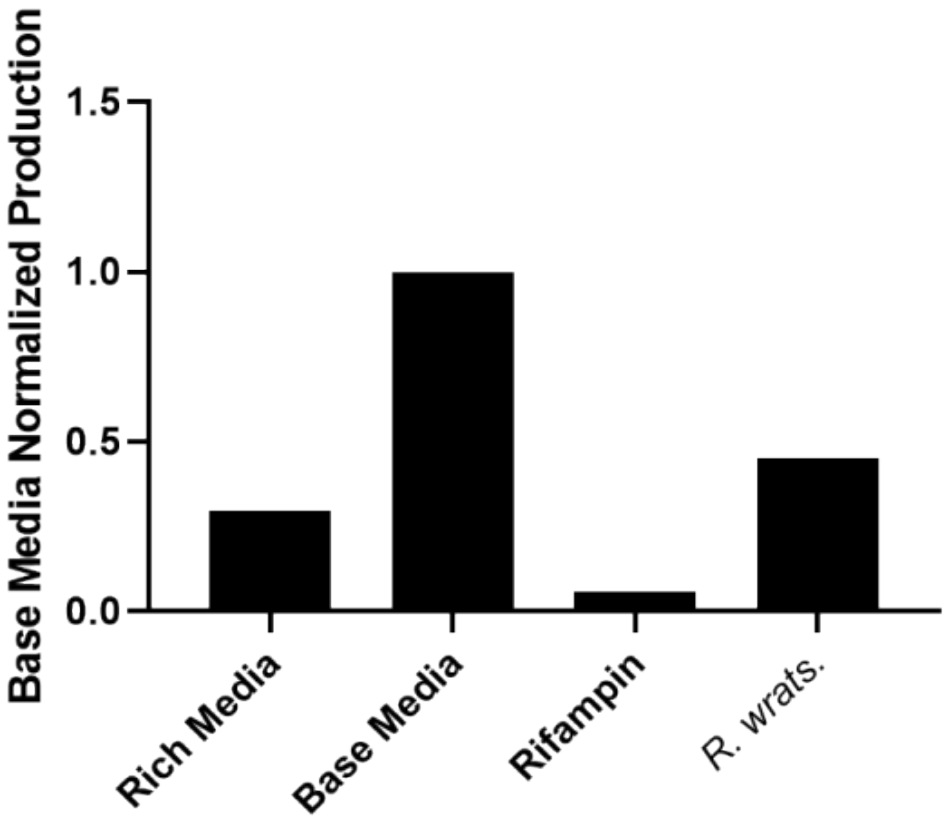
Supplemental figure 5. Natural product controls for cell phenotypes. A = aphidicolin. E = etoposide. N = ncodazole. R = rapamycin. S = staurosporine. V = vehicle. Numerals 1, 4, 16, 64 indicate fold dilution of *A. coloradensis* extract. Associated natural product phenotype control indicated by asterisks.



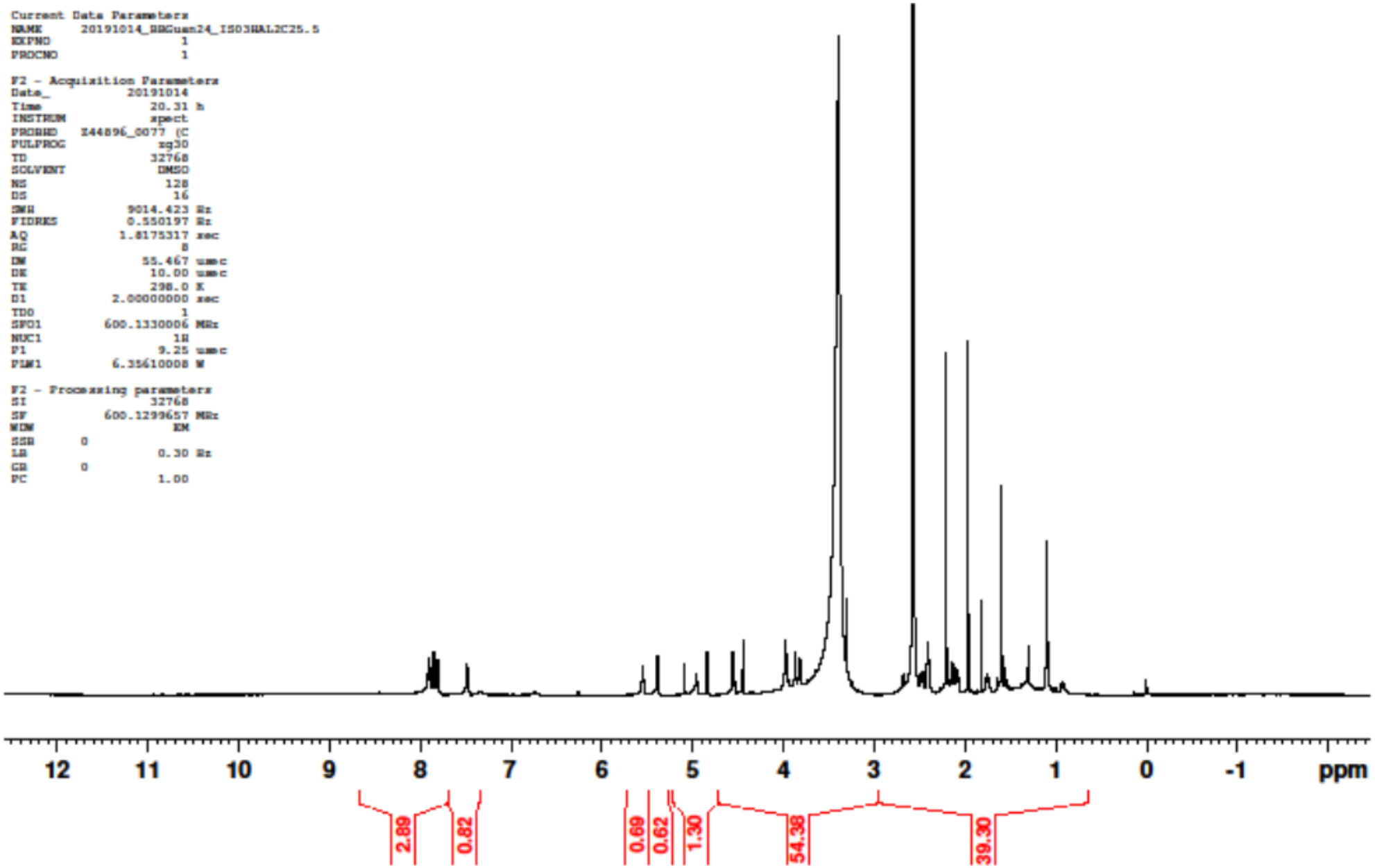
Supplemental figure 6. ^{1}H NMR of siderochelin in DMSO-d6.



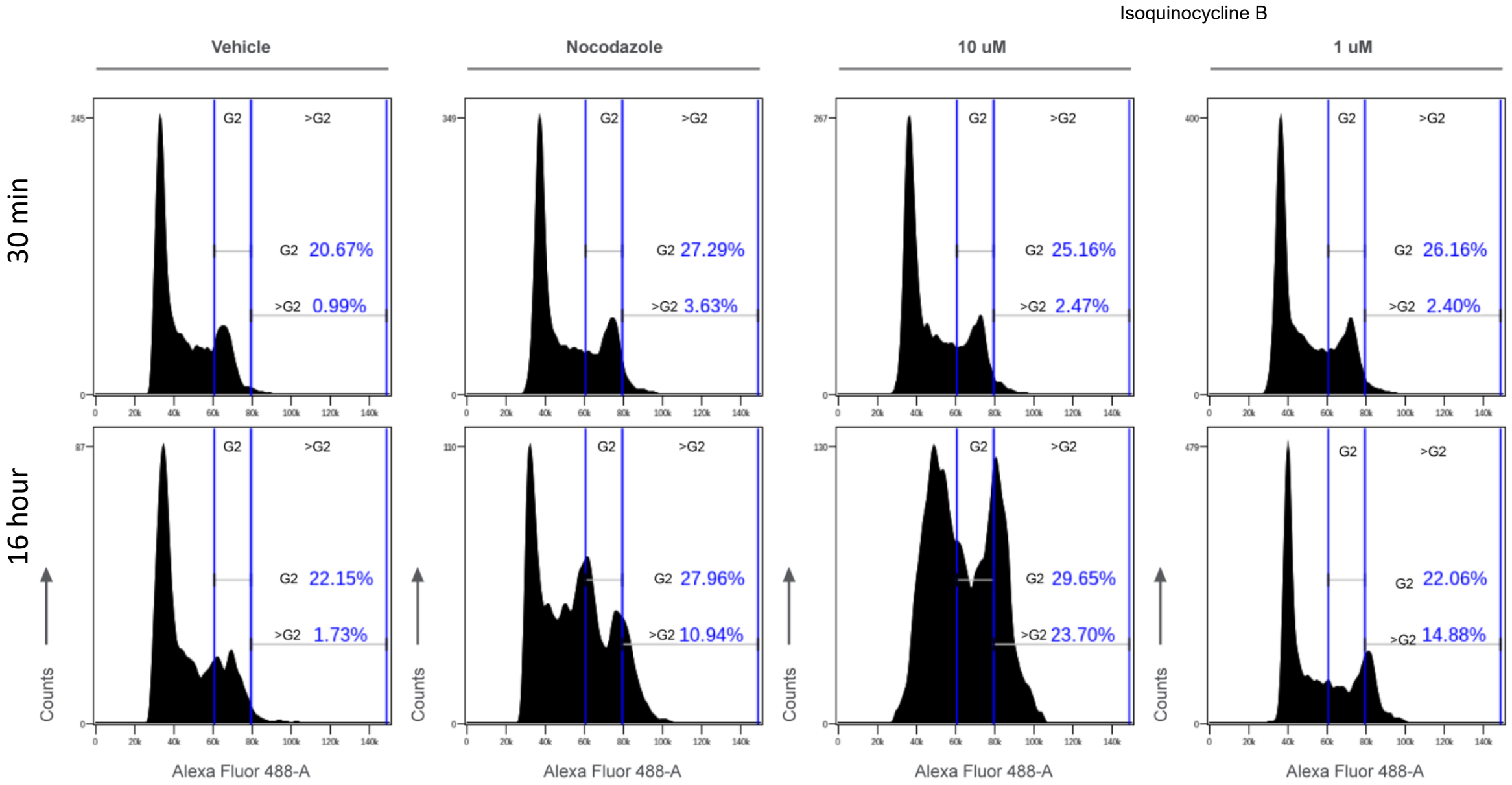
Supplemental Figure 7. Primary patient cells from different oncogenic niches exhibit different responses to siderochelin challenge. **A)** Patient bone marrow aspirates or leukapheresis samples were challenged with 10, 1, or 0.1 uM siderochelin for 24 hours then prepared for flow cytometry with a fluorescent antibody cocktail of indicated markers. **B)** Patient cells were gated for viable, singlets then into blast, lymphoid, and myeloid subsets using CD45 and SSC. **C)** Responses of aspirate and luekapheresis samples to siderochelin are shown as transparent histrograms of the 95th percentile of the median fluorescent intensity normalized to vehicle control (top row). **D)** Percent in gate for each indicated injury marker in blast (red), lymphoid (blue), and myeloid (purple) cell subsets.



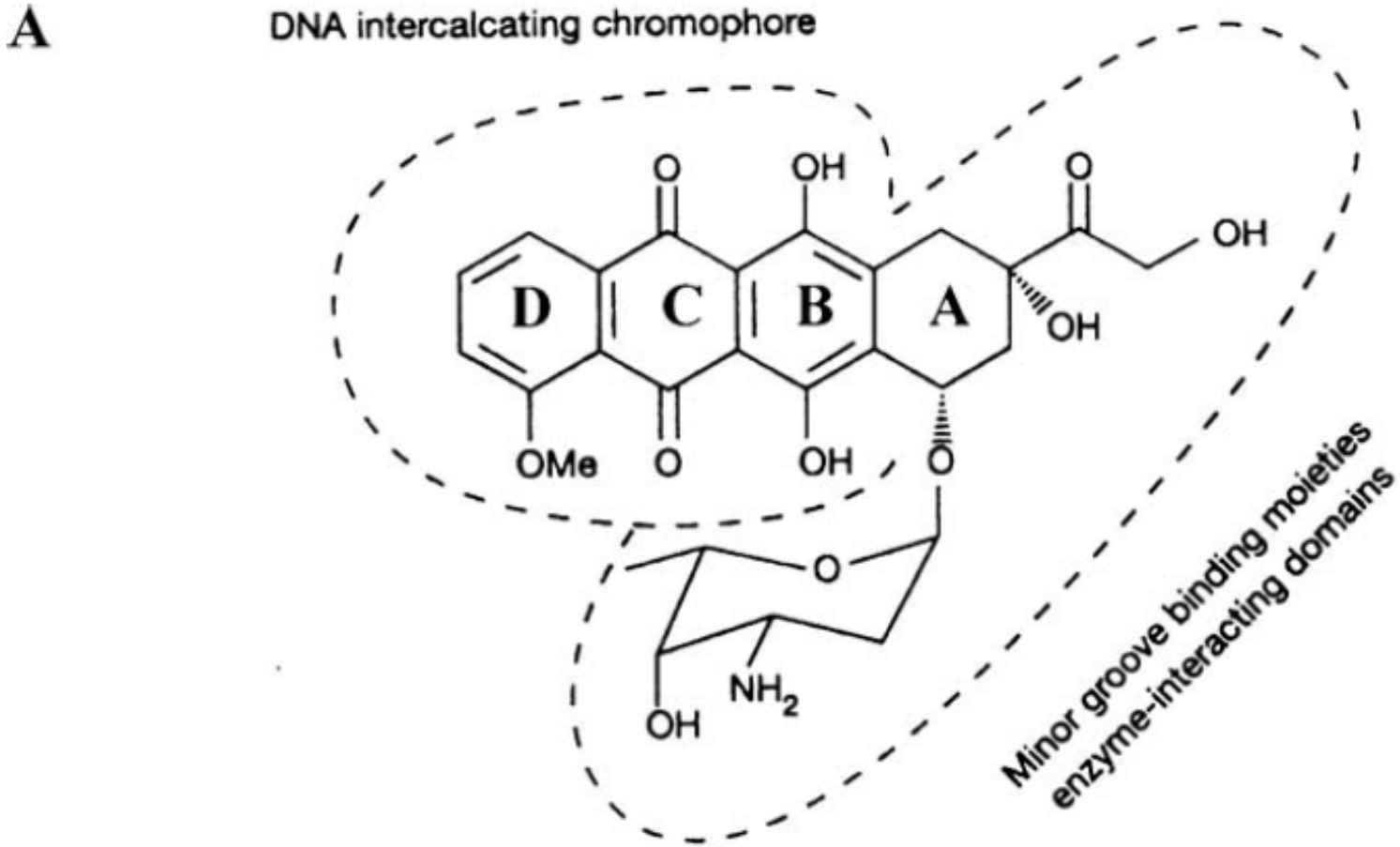
Supplemental figure 8. Normalized production of isoquinocycline B among culture conditions.



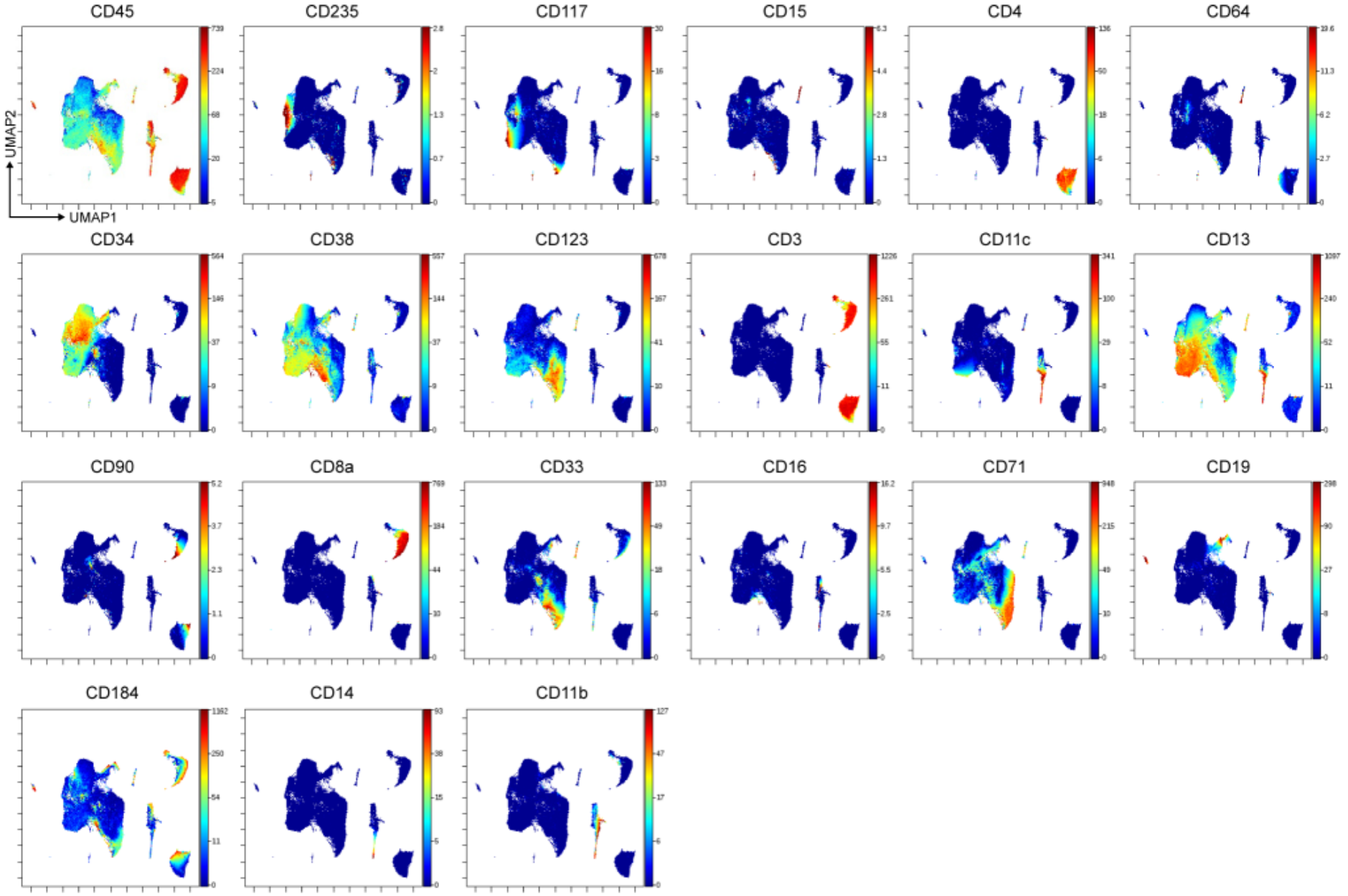
Supplemental figure 9. ^{1}H NMR of isoquinocycline B in DMSO-d6.



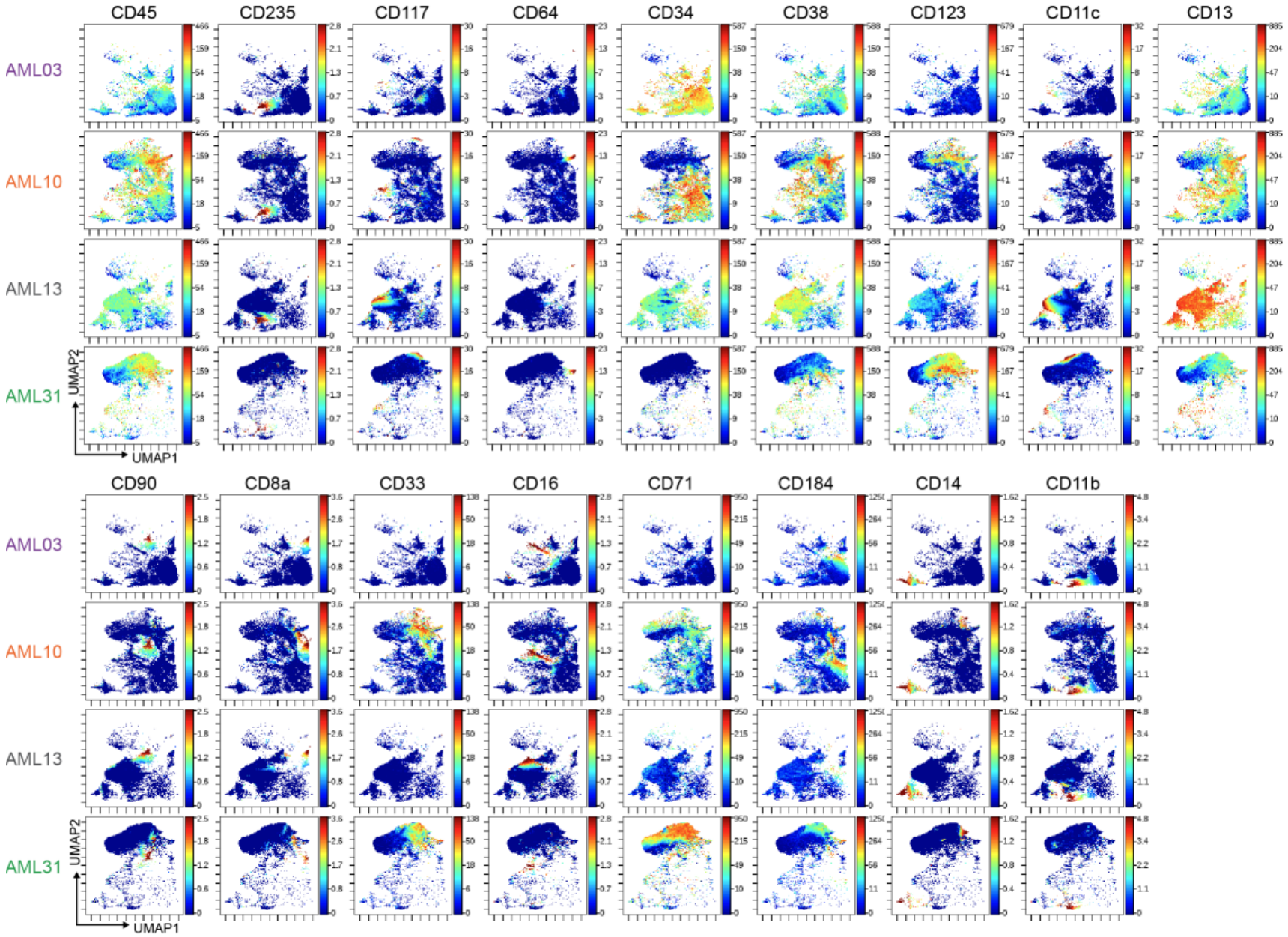
Supplemental figure 10. Isoquinocycline b increases DNA content over G2 in MV411 cell line after sixteen- hour challenge. Nocodazole positive control used to indicate G2 and >G2 gates.



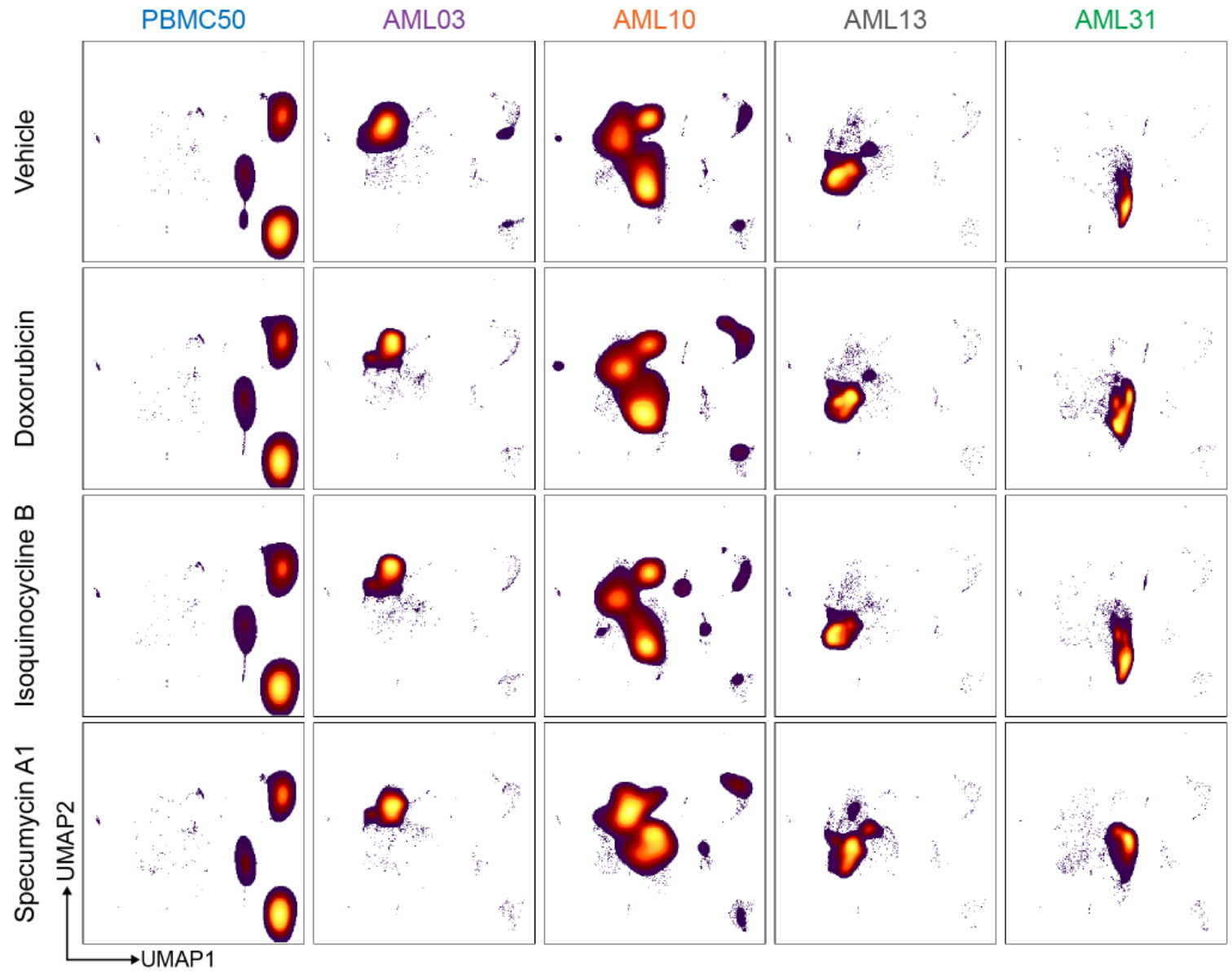
Supplemental figure 11. Isoquinocycline b interacting regions



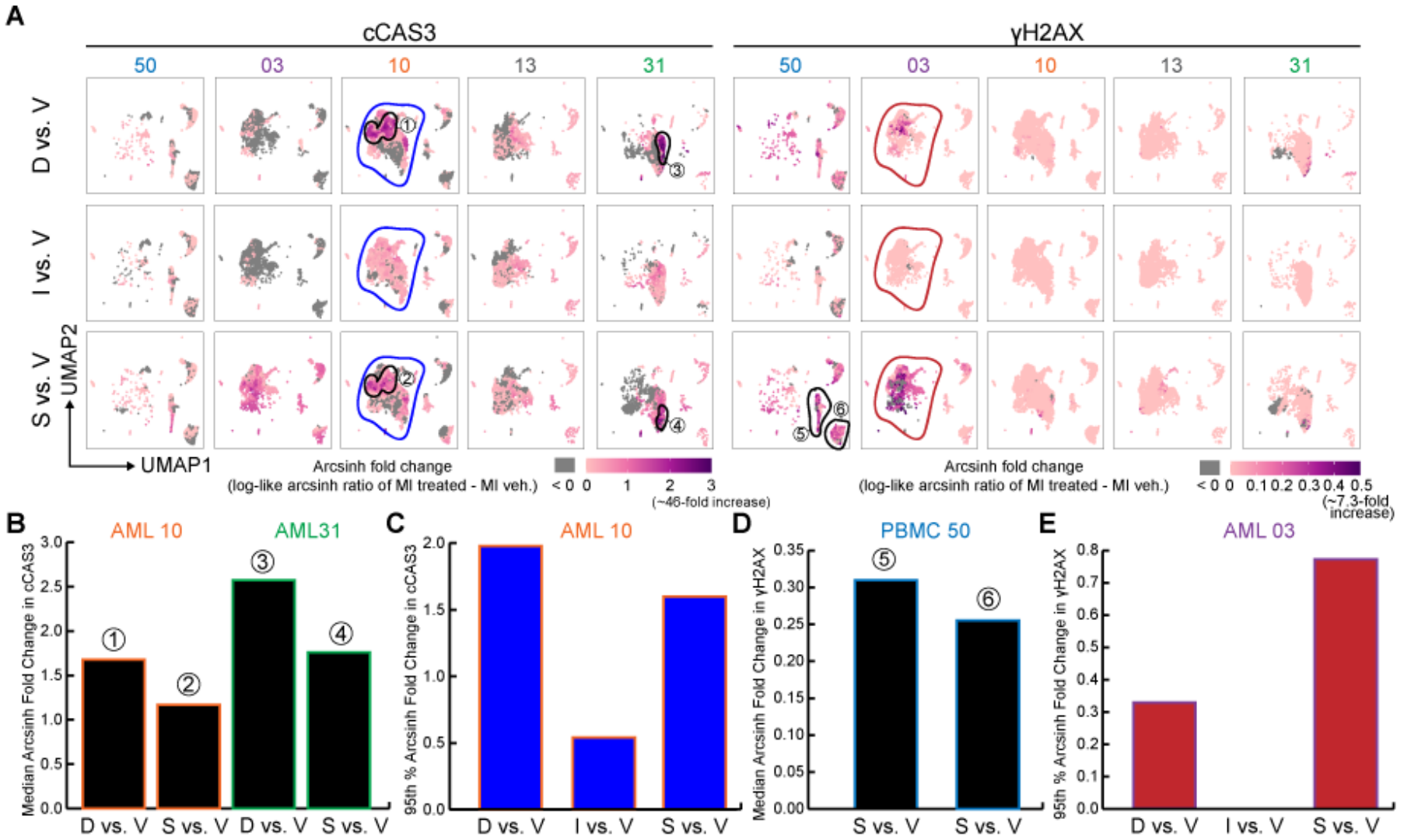
Supplemental Figure 12. Surface marker intensity values overlaid on UMAP were used to identify cell subsets. Plot depicting the result of performing a UMAP on the CyTOF data for five patients shown in Figure 6 and coloring based on intensity measurements for each of the 22 cell surface markers tested. Each readout is on its own scale as seen in the legend on the right side of each plot.



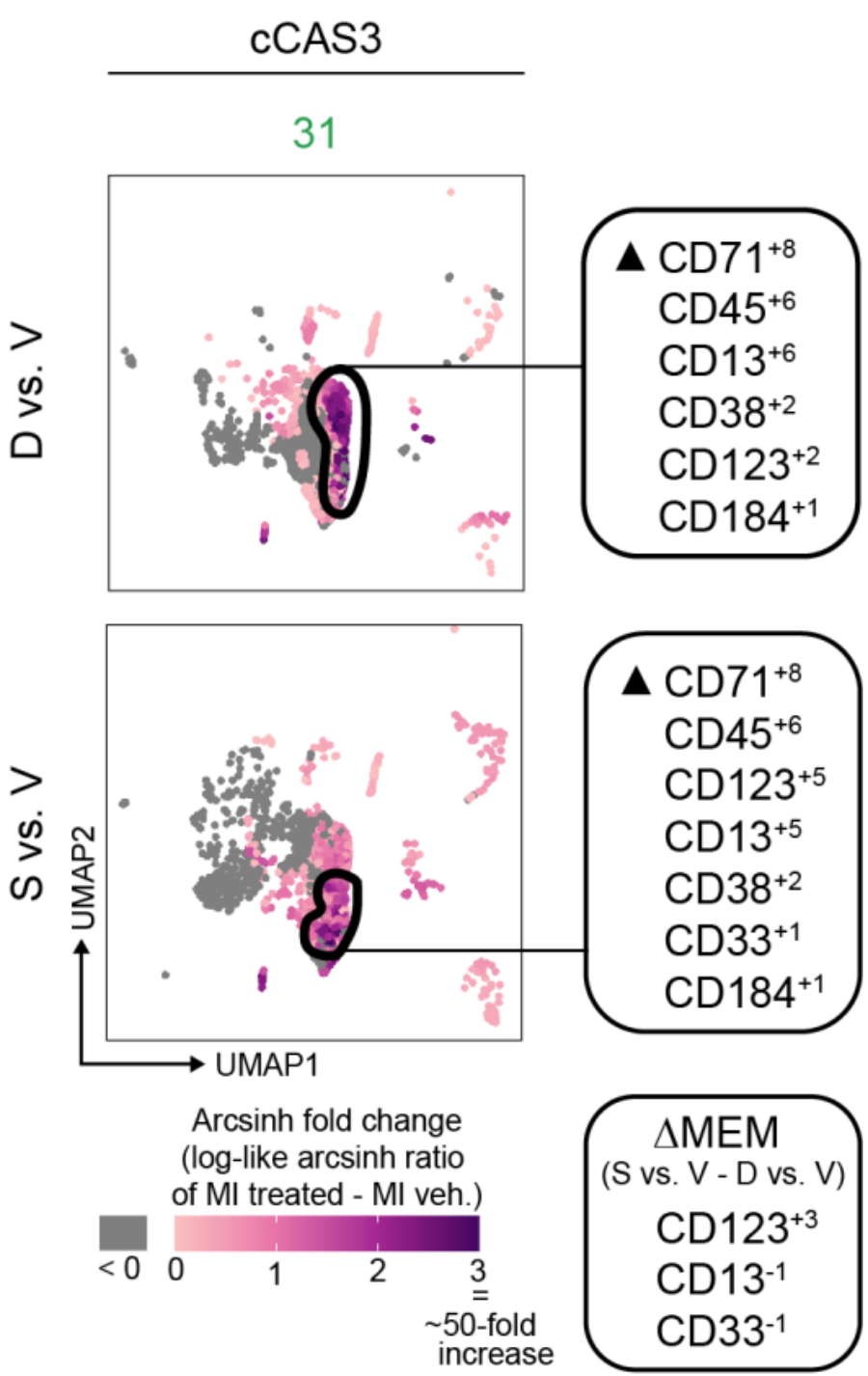
Supplemental Figure 13. Surface marker intensity values overlaid on UMAP of blasts only reveals phenotypic differences between patient blast cells. A new UMAP with corresponding x and y axes was generated using the 17 depicted cell surface markers and the cells within blast cell populations. Plots are colored based on intensity measurements for each of the 17 surface markers. Each readout is on its own scale as seen in the legend on the right side of each plot.



Supplemental figure 14. UMAP effectively separates AML blasts from non-malignant leukocytes. Contour plots depicting UMAP analysis performed on the three anthracyclines and vehicle in all five donors. Cells are color coded based on density with 2% of cells per contour.



Supplemental Figure 15. Quantifying cCAS3 and γH2AX for blasts and cell subsets guides comparisons across treatments and patients. **(A)** The KNN-fold change in median intensity values of each anthracyclines compared to vehicle for γH2AX and c-CAS3, respectively from left to right as depictied in Figure 6C annotated with cell subsets quantified in (B) - (E). Median intensity values are scaled by the log-like arcsinh fold change of anthracycline treated cells minus vehicle treated cells. Individual dots are colored where grey indicates a negative fold change value, blue indicates a fold change of zero and red indicates the highest possible fold change. **(B)** Barplot depicting the median arcsinh fold change in cCAS3 for populations 1-4 circled in (A). **(C)** Barplot depicting the 95th percentile fold change in cCAS3 for the blast cells of the specumycin, isoquinocycline, and doxorubicin vs. vehicle comparison, respectively, circled in blue in (A). **(D)** Barplot depicting the median arcsinh fold change in γH2AX for populations 5 and 6 circled in (A). **(E)** Barplot depicting the 95th percentile fold change in γH2AX for the blast cells of the specumycin, isoquinocycline, and doxorubicin vs. vehicle comparison, respectively, circled in red in (A).



Supplemental Figure 16. Marker Enrichment Modeling (MEM) labels reveal differences in cCAS3 high subsets in response to doxorubicin and specumycin treatment in AML31. Fold change on UMAP plots from Figure 6F with the largest population of the top quartile of arcsinh fold change in cCAS3 values circled. MEM was applied to each circled population and the MEM labels are supplied on the right side. The difference between the two MEM labels ("ΔMEM") is supplied below.