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AACR 2021

CHAMPIONS ONCOLOGY

Creating Greater Certainty in the Fight Against Cancer

In Vitro and In Vivo Model for Evaluation of Novel Therapeutic Agents in Patient derived-Lymphoblastic Leukemia (B-ALL)

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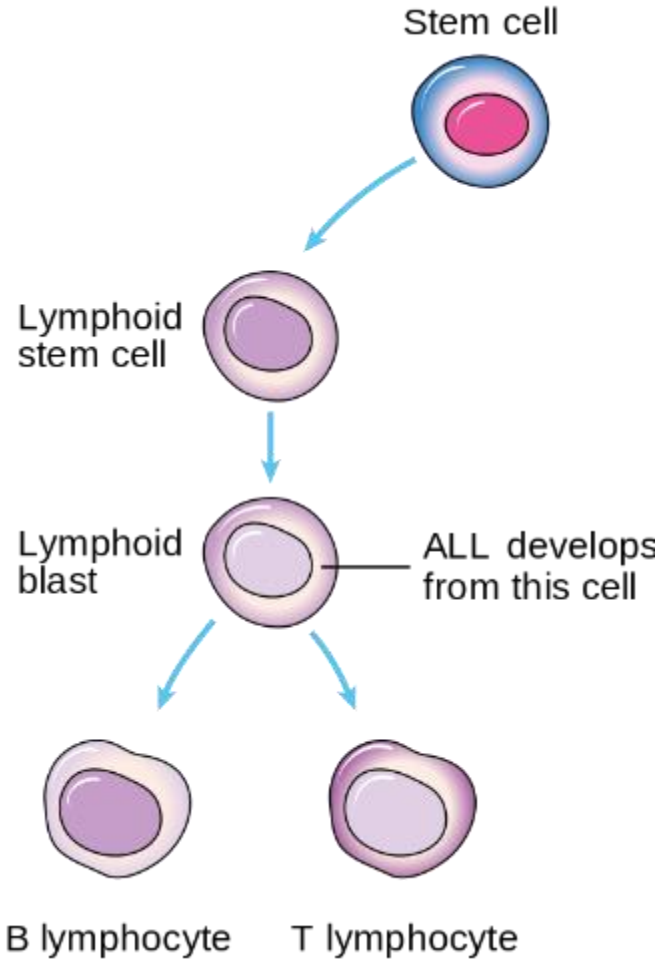
B Cell Acute Lymphoblastic Leukemia (B-ALL)

- Malignant transformation and proliferation of lymphoid progenitors in peripheral blood, bone marrow, and extramedullary sites.
- Prevalent in children and young adults
- 6150 new cases and 1520 deaths
- Relapse and resistant cases
- Drug screening platform - ex vivo and in vivo



Champions B-ALL Model Characterization

- **Clinical Characteristics:**
  - **Age, Gender, Race**
- **Precursor B Cell ALL**
- **De Novo**
- **MYC, ATM, NRAS, PTPN11, RUNX1**
- **Immunophenotyped**
- **t(9;22) [BCR-ABL]+: 13 models**
- **t(9;22) [BCR-ABL]-: 11 models**

Champions Models	Sample Type	Status Collection	Cytogenetics Abnormality	Clinical Flow Cytometry Phenotype
CTG-2406	Pheresis	Unknown	N/A	N/A
CTG-2447	Pheresis	Unknown	N/A	CD10 bright +CD19+CD20 dim, variable, small subset + CD34 dim, variable, small subset +CD79+HLA-DR bright +TdT+
CTG-2409	Pheresis	De Novo	42,XX,+8,t(9;22)(q34;q11.2),+der(22)t(9;22)[1]/46,XX[1]	CD5-CD10+CD13-CD14-CD15-CD19+CD20 var +CD33-CD34 var +CD56-CD64-CD79 a +HLA-DR+TdT var +
CTG-3682	PB-MNC	De Novo	42,XX,+8,t(9;22)(q34;q11.2),+der(22)t(9;22)[1]/46,XX[1]	CD5-CD10+CD13-CD14-CD15-CD19+CD20 var +CD33-CD34 var +CD56-CD64-CD79 a +HLA-DR+TdT var +
CTG-3683	PB-MNC	De Novo	46,XY[5] (Normal)	CD5-CD10+CD13-CD14-CD15-CD19+CD20dim/variable +CD33CD34+CD56CD64CD79+HLADR+TdTdim/variable +
CTG-3684	PB-MNC	De Novo	Normal	CD5-CD10 var +CD13 var +CD14-CD15-CD19 var+ CD20-CD33 var+CD34+CD38 var +CD56-CD64-CD79 var +HLA-DR+TdT+
CTG-2707	Pheresis	De Novo	45,XY,-7,t(9:22)(q34;q11.2)[20]	CD5-CD10+CD13+CD14-CD15-CD19+CD20-CD33 var + CD34 var +CD56-CD64-CD79+HLA-DR bright +TdT+
CTG-3685	Pheresis	De Novo	46,XX,t(4;11)(q21;q23)[6]/46,XX[5]	CD5-CD10-CD13-CD14-CD15 aberrant expression + CD19+CD20-CD33-CD34-CD38+CD56-CD64-CD79+ HLA-DR+TdT+
CTG-3686	PB-MNC	De Novo	47,XY,del(7)(p15),+add(8)(p11.2),der(9)del(9)(p13)t(9;22)(q34;q11.2),der(22)t(9;22)[7]/ 46,XY[1]	CD5-CD10+CD13-CD14-CD15-CD19+CD20 var +CD33-CD34+CD38-CD56-CD64-CD79+HLA-DR+TdT+

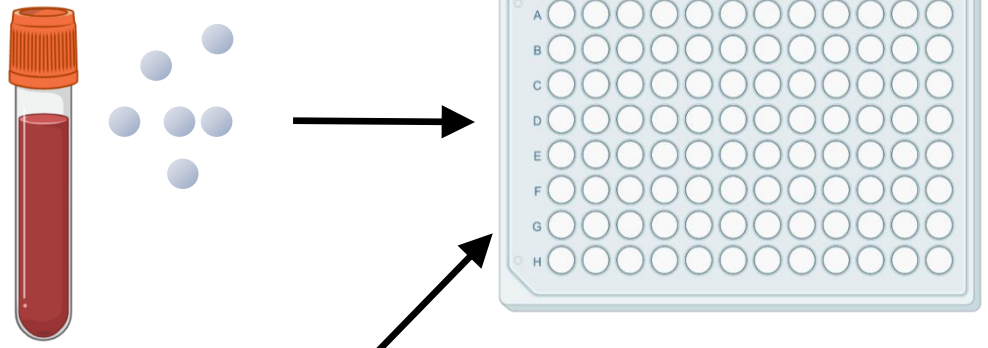
Development of ex vivo and in vivo platform for evaluation of novel therapeutics in patient-derived B-ALL

Schematic Representation of the Ex Vivo Study

Patient-derived B-ALL models

Drug

Specimen Input:
- PBMC
- Leukapheresis
- Bone marrow sample
- PDX explant



Enriched Growth Media

Assay Format
- 3 day assay

Applications
- Drug Screen
- Biomarker Discovery
- Mechanism of Action
- In vivo Model Selection

Study Endpoints:
- Proliferation
- Tumor Cytotoxicity
- Apoptosis
- Phenotyping

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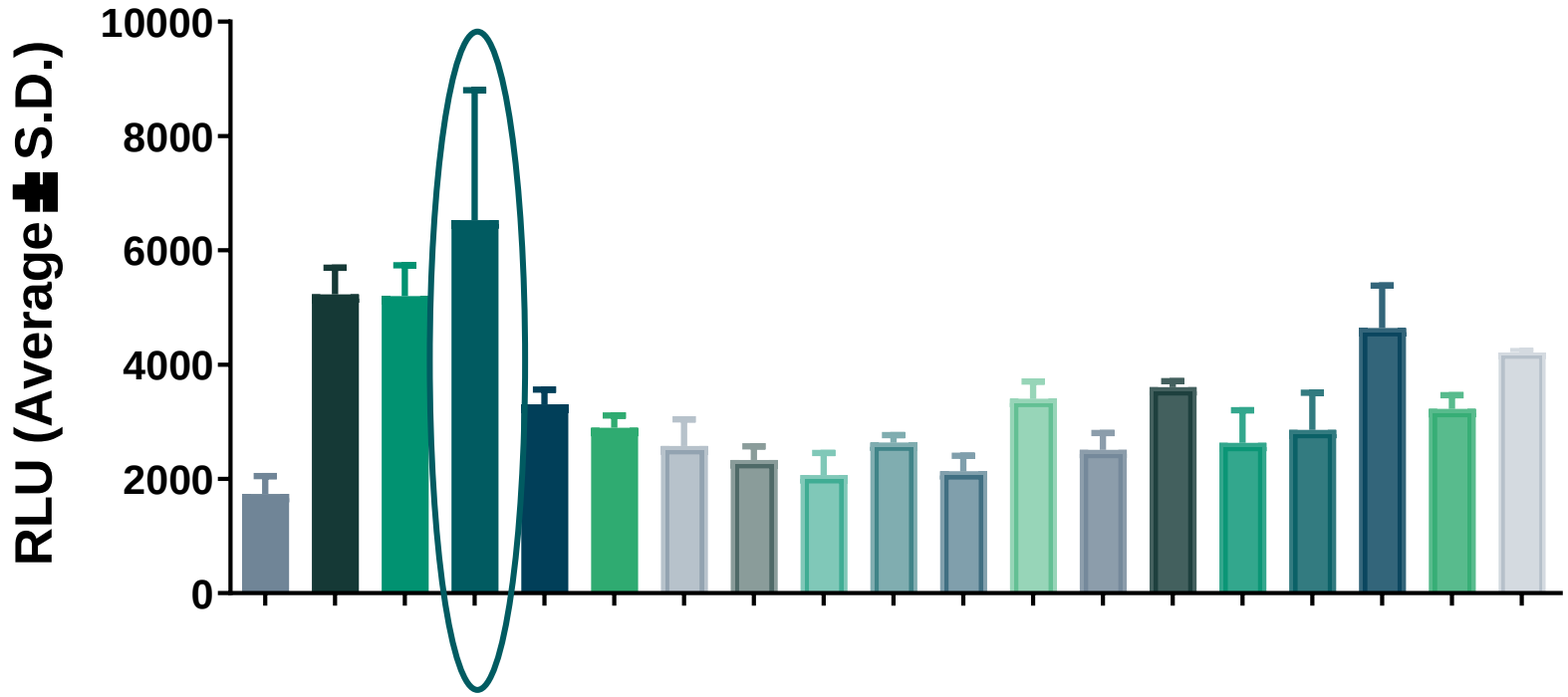
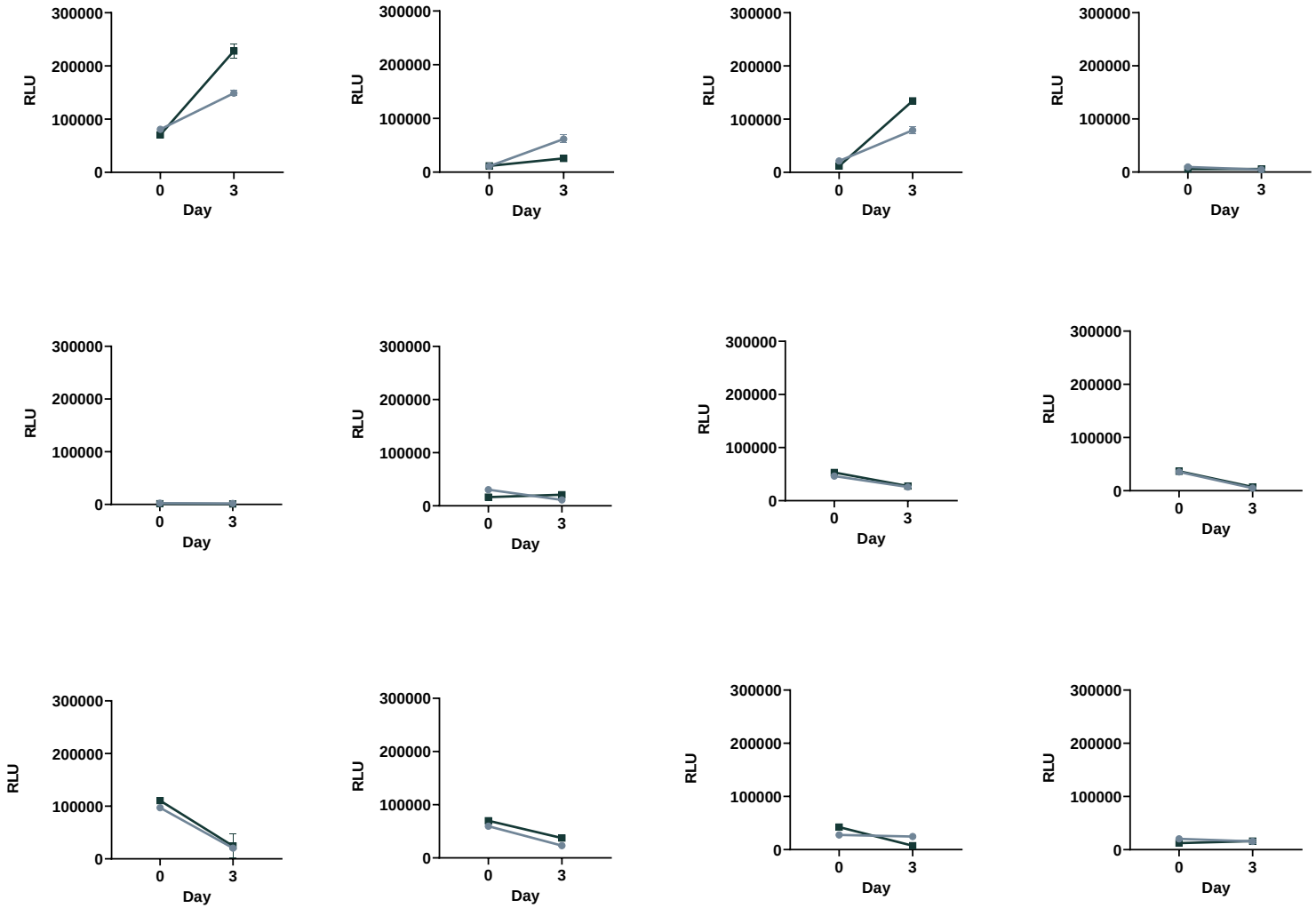
Evaluation of Culture Conditions for 3 day B-ALL cultures

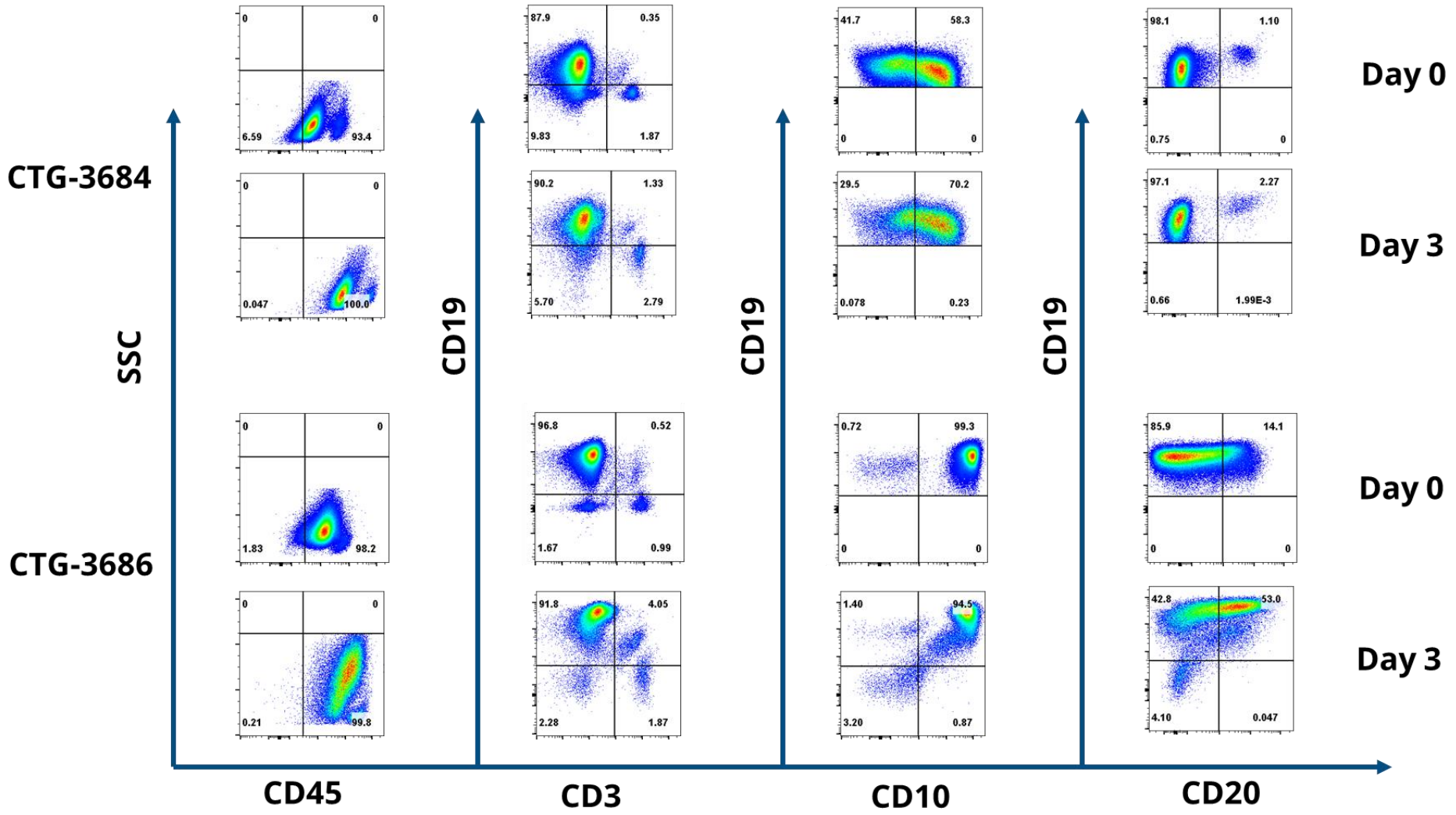


Selection of media, supplements and other culture conditions (representative of several studies with similar results across models)

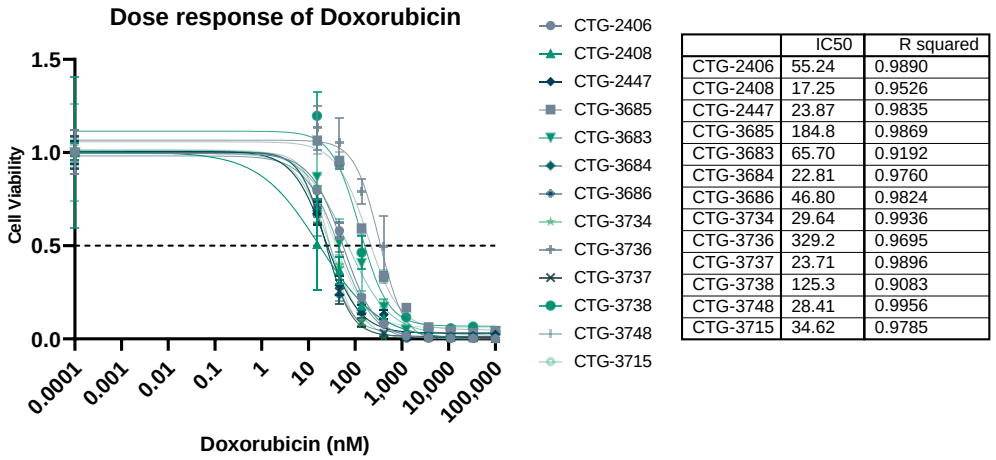
Reproducible Performance in Proliferation/ Survival in Enriched Media



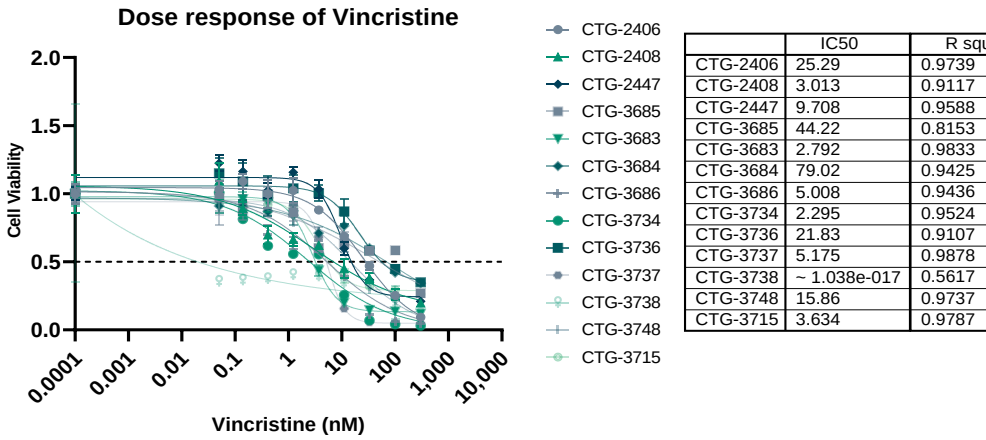
Models Maintain B-ALL Phenotype in Culture



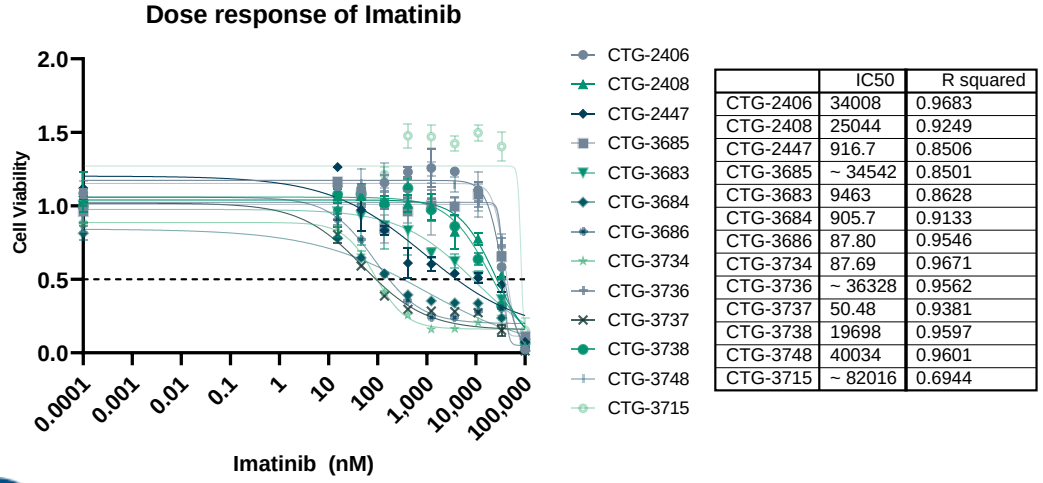
Responsiveness of B-ALL to Standard of Care Treatment in Ex Vivo Platform



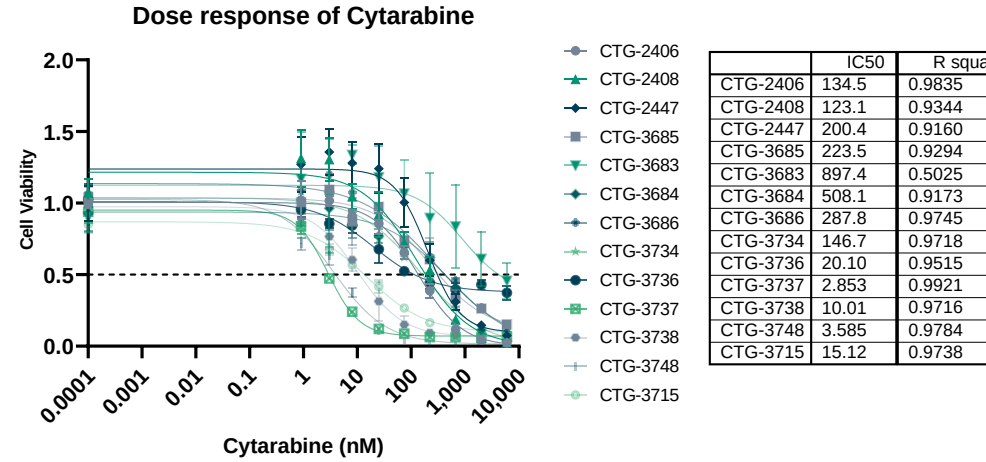
	IC50	R squared
CTG-2406	55.24	0.9890
CTG-2408	17.25	0.9526
CTG-2447	23.87	0.9835
CTG-3685	184.8	0.9869
CTG-3683	65.70	0.9192
CTG-3684	22.81	0.9760
CTG-3686	46.80	0.9824
CTG-3734	29.64	0.9936
CTG-3736	329.2	0.9695
CTG-3737	23.71	0.9896
CTG-3738	125.3	0.9083
CTG-3748	28.41	0.9956
CTG-3715	34.62	0.9785



	IC50	R squared
CTG-2406	25.29	0.9739
CTG-2408	3.013	0.9117
CTG-2447	9.708	0.9588
CTG-3685	44.22	0.8153
CTG-3683	2.792	0.9833
CTG-3684	79.02	0.9425
CTG-3686	5.008	0.9436
CTG-3734	2.295	0.9524
CTG-3736	21.83	0.9107
CTG-3737	5.175	0.9878
CTG-3738	~ 1.038e-017	0.5617
CTG-3748	15.86	0.9737
CTG-3715	3.634	0.9787



	IC50	R squared
CTG-2406	34008	0.9683
CTG-2408	25044	0.9249
CTG-2447	916.7	0.8506
CTG-3685	~ 34542	0.8501
CTG-3683	9463	0.8628
CTG-3684	905.7	0.9133
CTG-3686	87.80	0.9546
CTG-3734	87.69	0.9671
CTG-3736	~ 36328	0.9562
CTG-3737	50.48	0.9381
CTG-3738	19698	0.9597
CTG-3748	40034	0.9601
CTG-3715	~ 82016	0.6944



	IC50	R squared
CTG-2406	134.5	0.9835
CTG-2408	123.1	0.9344
CTG-2447	200.4	0.9160
CTG-3685	223.5	0.9294
CTG-3683	897.4	0.5025
CTG-3684	508.1	0.9173
CTG-3686	287.8	0.9745
CTG-3734	146.7	0.9718
CTG-3736	20.10	0.9515
CTG-3737	2.853	0.9921
CTG-3738	10.01	0.9716
CTG-3748	3.585	0.9784
CTG-3715	15.12	0.9738

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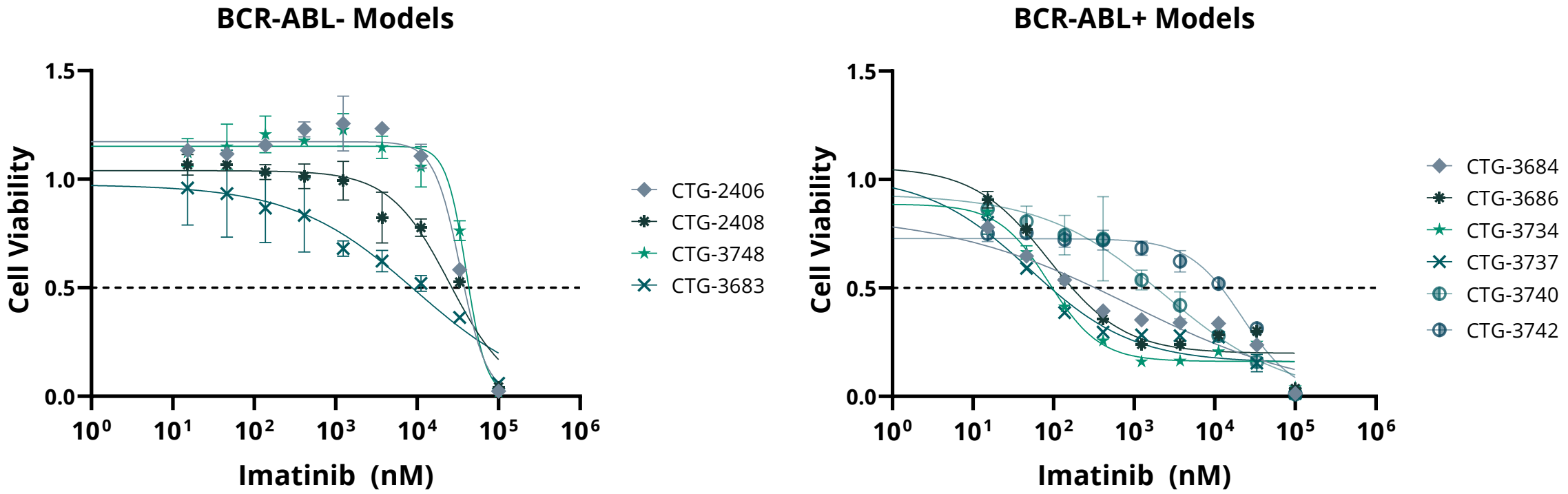
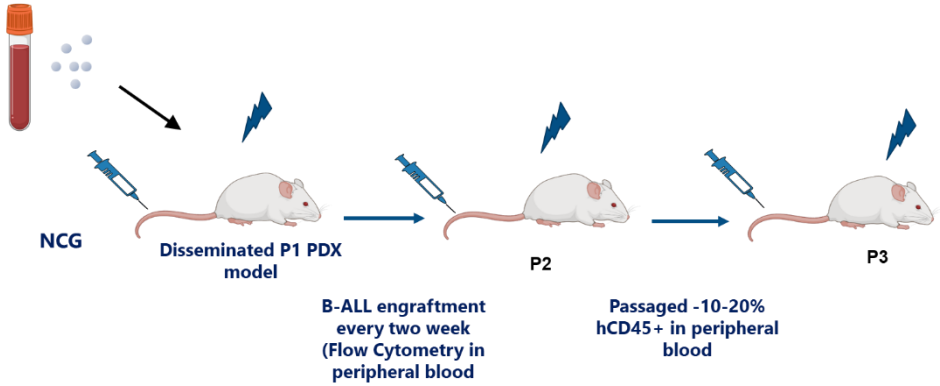
Mutational Status Drives Differential Response to Imatinib

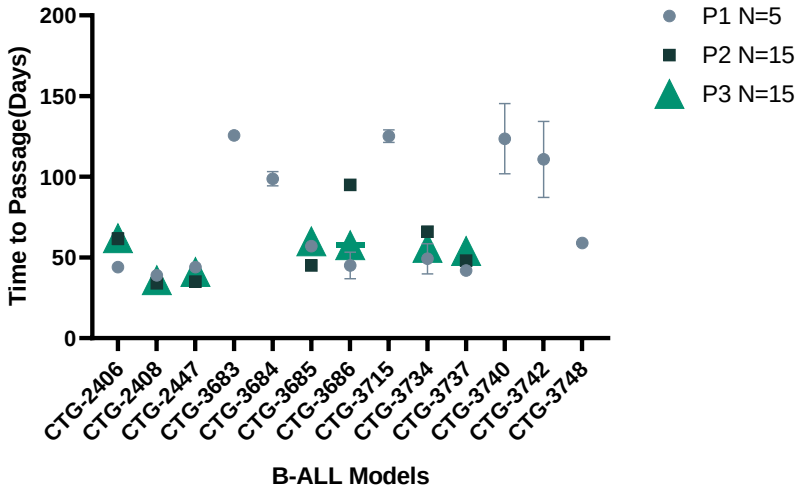


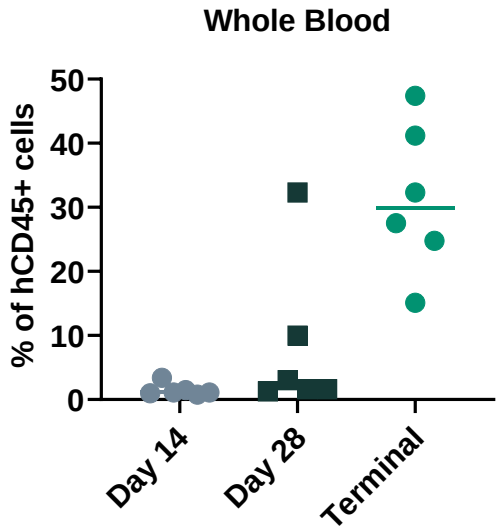
Champions' B-ALL PDX Development for In Vivo Drug Efficacy Study

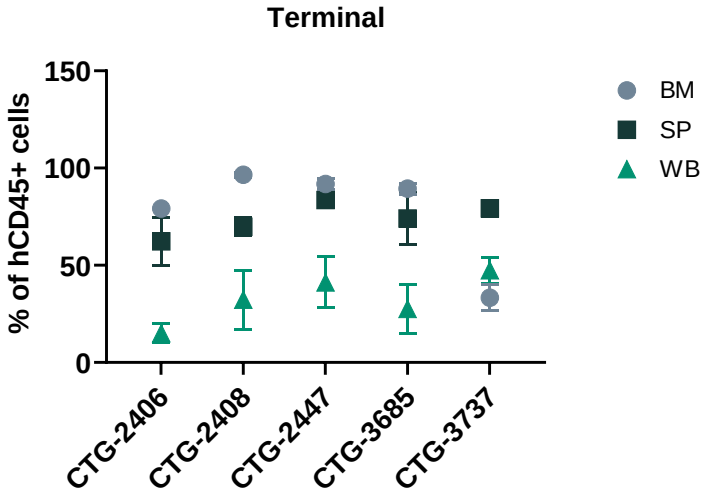
Engraftment and Kinetics of Primary B-ALL cells In Vivo



Schematic representation of B-ALL PDX development

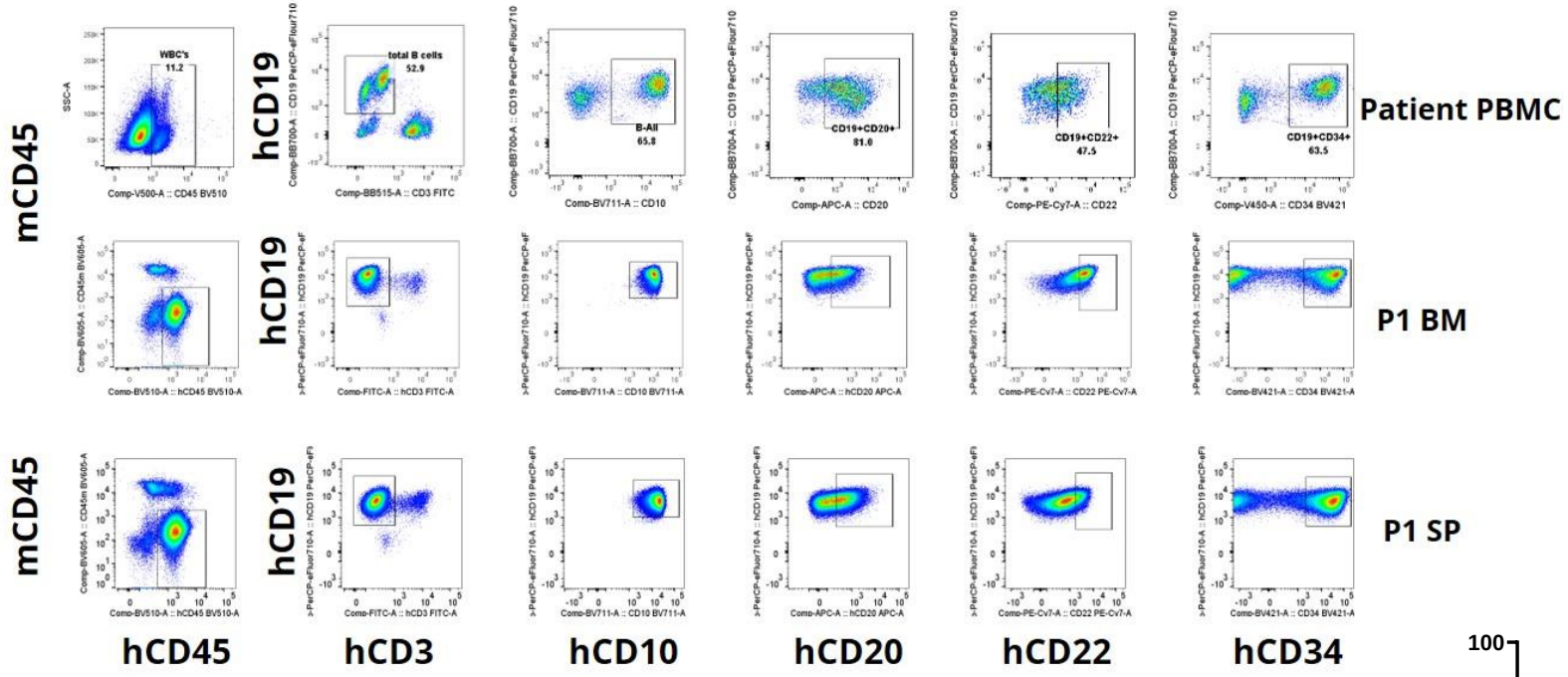


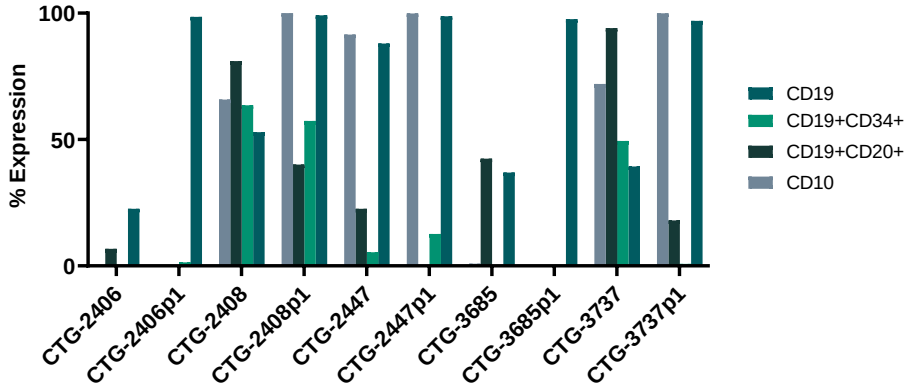




Immunophenotype of Patient Sample is Comparable to P1 BM and Spleen Cells

CTG-2408





Comparable Ex Vivo Response of Primary B-ALL and Passaged B-ALL PDX (P2) Models

	Model A CTG-2406		Model B CTG-2408		Model C CTG-2447	
SOC	Patient Specimen	B-ALL PDX Explant (Splenocytes)	Patient Specimen	B-ALL PDX Explant (Splenocytes)	Patient Specimen	B-ALL PDX Explant (Splenocytes)
Doxorubicin	IC50 – 32.28nM R^2 -0.99	IC50 – 23.82nM R^2 -0.99	IC50 – 17.25nM R^2 -0.95	IC50 – 0.56nM R^2 -0.95	IC50 – 23.87nM R^2 -0.98	IC50 – 15.09nM R^2 -0.99
Vincristine	IC50 – 20.27nM R^2 -0.96	IC50 – 6.97nM R^2 -0.96	IC50 – 3.013nM R^2 -0.91	IC50 – 1.579nM R^2 -0.84	IC50 – 9.708nM R^2 -0.95	IC50 – 31.77nM R^2 -0.98
Cytarabine	IC50 – 828.4nM R^2 -0.95	IC50 – 828.8nM R^2 -0.90	IC50 – 123.1nM R^2 -0.93	IC50 – 473.7nM R^2 -0.88	IC50 – 200.4nM R^2 -0.916	IC50 – 83.85nM R^2 -0.96
Imatinib	IC50 – 21.16uM R^2 -0.94	IC50 – 30.10uM R^2 -0.93	IC50 – 25.04uM R^2 -0.92	No Response	IC50 – 0.916uM R^2 -0.85	IC50 – 3.755uM R^2 -0.85

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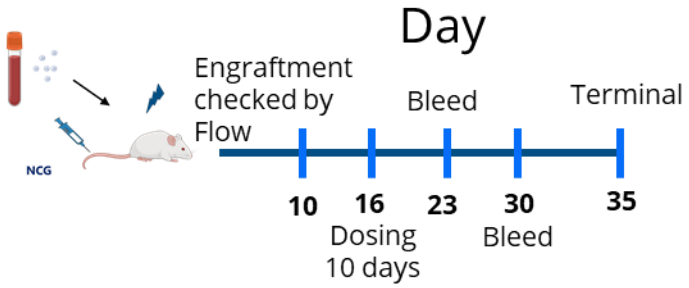
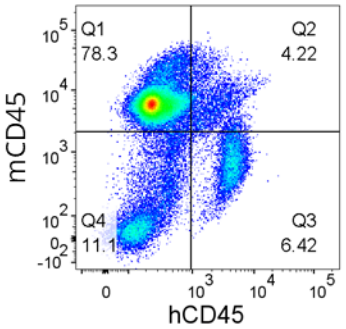
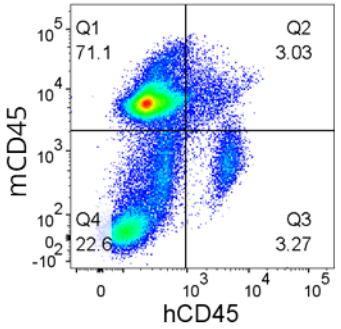
Venetoclax Treatment Inhibits Proliferation of Patient-derived B-ALL Cells (CTG-2408) In Vivo



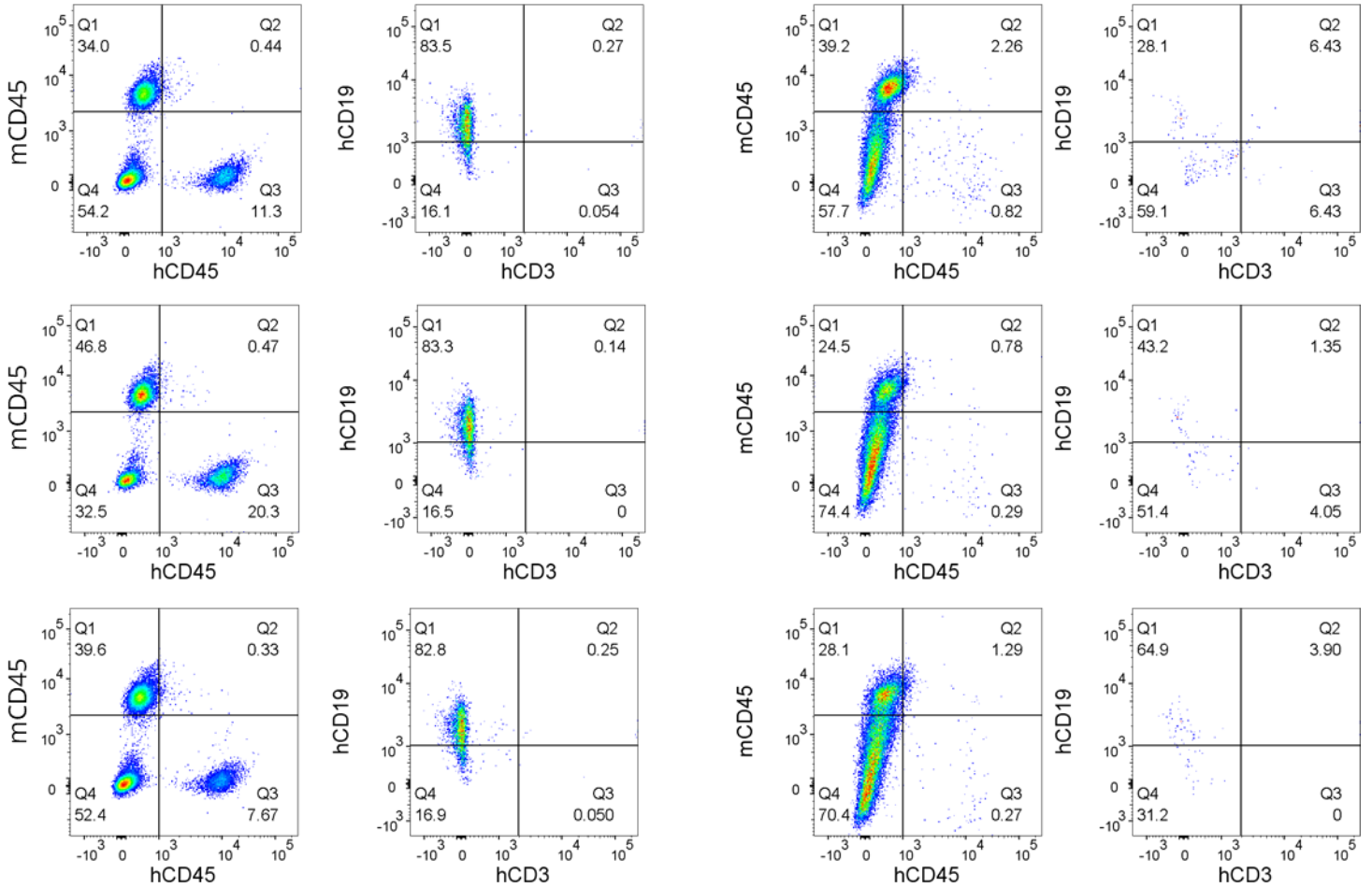




Bone Marrow Day 10 before dosing

Vehicle Treated

Venetoclax Treated



Peripheral Blood Day 7 of treatment

Summary & Next Steps

- Patient derived primary B-ALL cells survive and proliferate in enriched media.
- B-ALL models showed responsiveness to standard of care drugs in ex vivo platform. Interestingly, molecular subtyping (BCR-ABL+) demonstrated correspondence with drug response to imatinib in this platform.
- NCG mice support the engraftment and development of B-ALL disease initiating and leukemic cells in vivo.
- The passaged patient-derived preclinical xenograft model recapitulates the B-ALL disease.
- Venetoclax inhibits the proliferation of patient derived B-ALL cells in vivo suggesting that the patient-derived preclinical in vivo model can be used for drug efficacy studies.
- Passaged B-ALL models will provide a renewable source for both ex vivo and in vivo platforms for drug screening/drug discovery.
- WES and RNA-Seq is in progress for all models.

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