

Insights into the Cell-of-Origin of the Histiocytoses Using Patient-Derived Xenograft Models

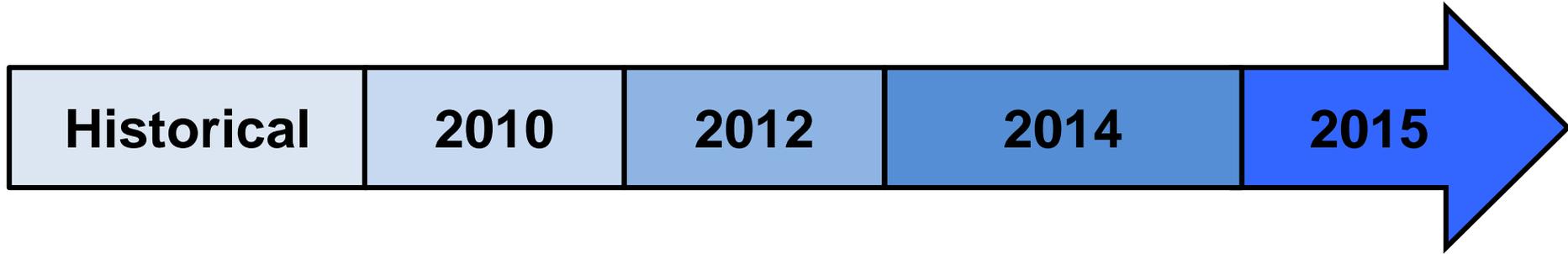
4th Annual International Erdheim-Chester Disease Medical Symposium
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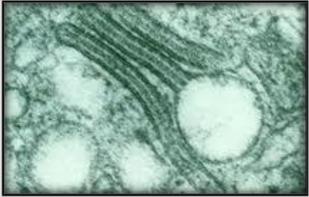
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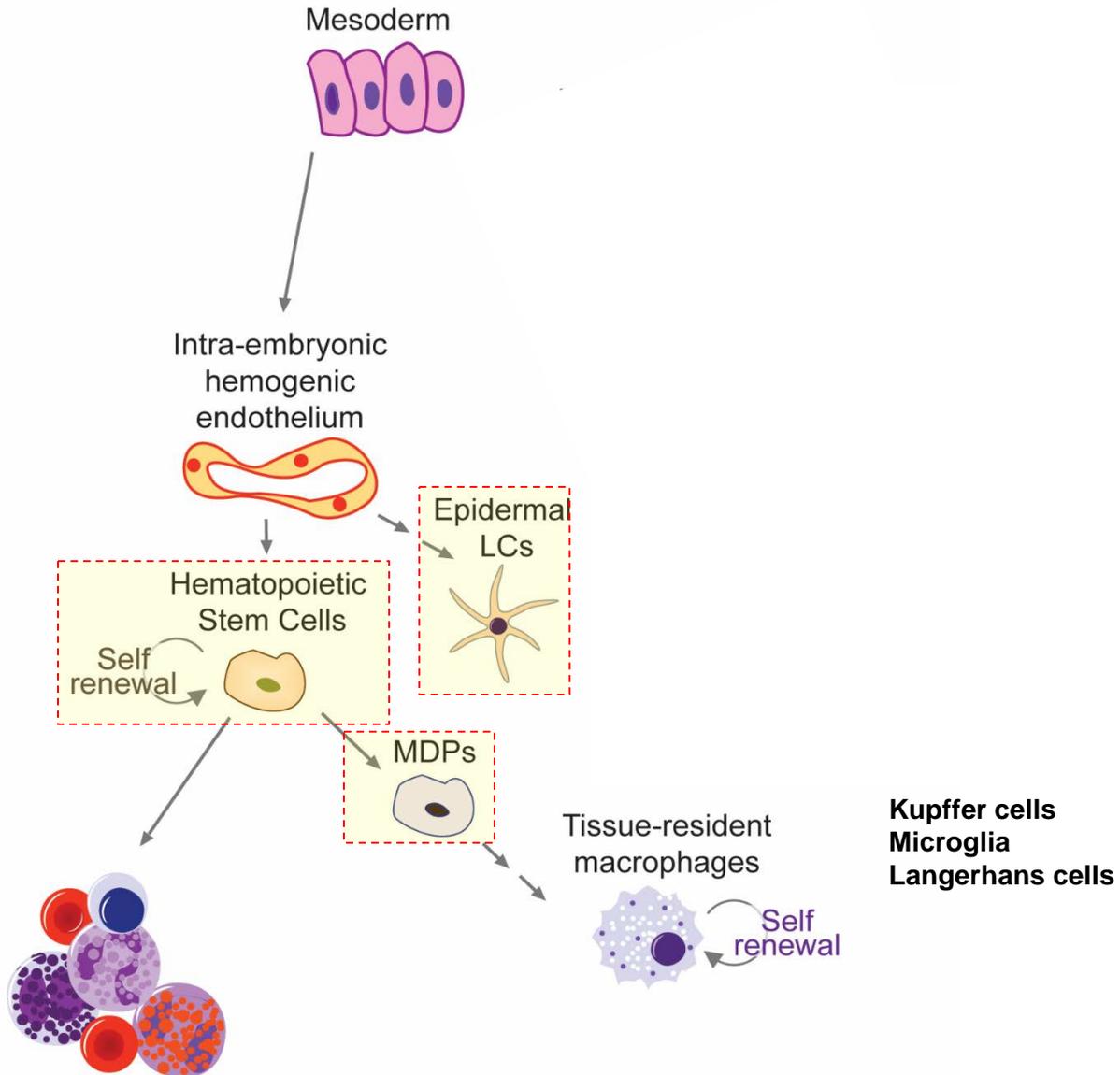


What Cells Give Rise to Histiocytoses?



<p>LCH arises from Langerhans cells (LCs)</p> <ul style="list-style-type: none"> - Shared antigenic markers - Birbeck granules 	<p>LCH cell Transcriptional profile more similar to monocyte-derived precursors than LCs</p>	<p>Epidermal LCs arise from fetal liver monocytes rather than bone marrow hematopoietic precursors</p>	<p>BRAF V600E detected in bone marrow precursors of high-risk BRAF V600E-mutated LCH patients</p>	<p>LCH and non-LCH neoplastic cells have distinct transcriptional profiles</p>
<p>Nezelof <i>et al. Biomedicine</i> 1973.</p>	<p>Allen <i>et al. J. Immunol.</i> 2010.</p>	<p>Hoeffel <i>et al. J. Exp. Med.</i> 2012.</p>	<p>Berres <i>et al. J. Exp. Med.</i> 2014.</p>	<p>Diamond, Durham, Haroche <i>et al. Cancer Discov.</i> 2015.</p>

Ontogeny of Macrophages and the Potential Cell(s)-of-Origin of Systemic Histiocytic Neoplasms



Cell-of-Origin Studies of Histiocytosis

- **Berres *et al.*** suggested LCH is a clonal disorder arising from HSPCs that acquire a somatic mutation in an oncogenic pathway linked to the histiocytoses
- ***BRAF* V600E mutation has not been detected in the CD34+ compartment of all *BRAF* V600E-mutated LCH patients**
- **Expression of *BRaf* V600E in the murine dendritic cell precursors does not recapitulate all phenotypic consequences of human LCH.**
 - Opens the possibility of alternate cells or origin for the systemic histiocytoses
 - Tissue-resident macrophages arising from yolk sac-derived EMPs
- **Comparable studies have not been published in ECD and other non-LCH neoplasms, and whether or not HSPCs from histiocytosis patients have functional self-renewal potential is unknown.**

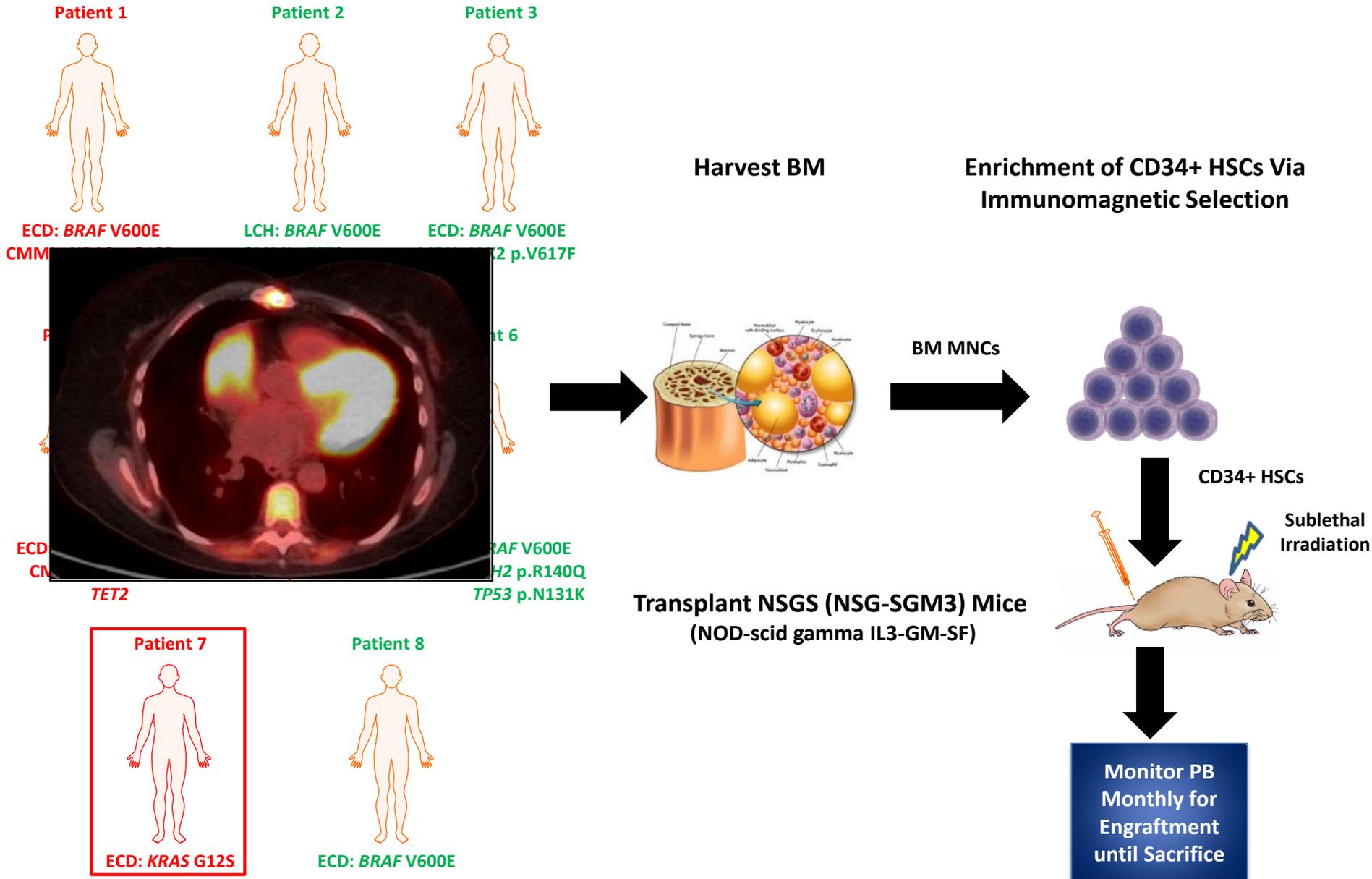
Experimental Questions

- Can hematopoietic stem and progenitor cells from systemic histiocytoses patients functionally give rise to these disorders?
- Can we generate patient-derived xenograft models of histiocytic neoplasms for further functional analyses or *in vivo* treatment?

Diagnostic and Mutational Data for the Eight Xenografted Histiocytosis Patient Samples

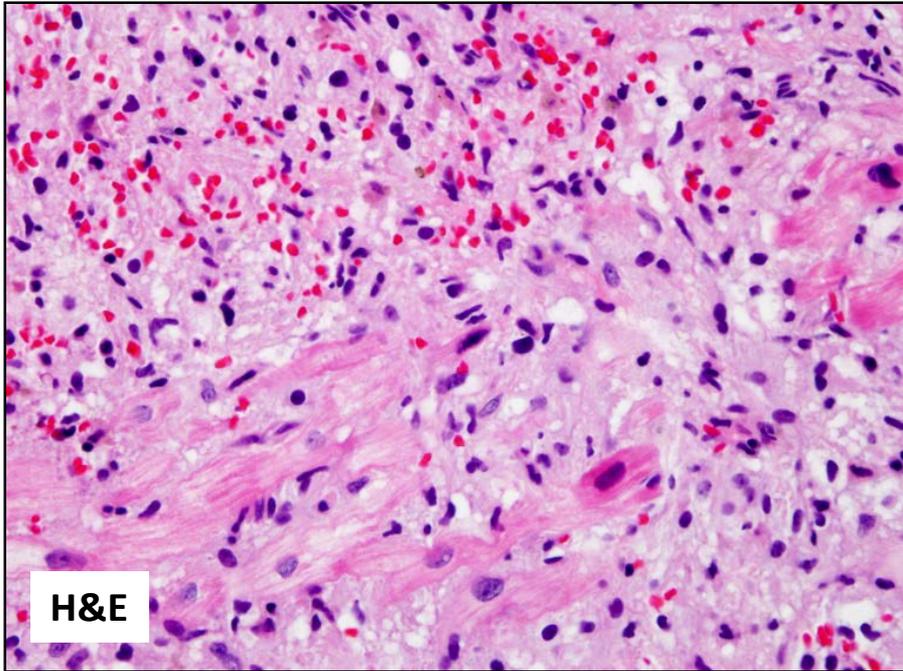
Patient ID	Histiocytic Neoplasm	Histiocytic Mutation	WHO-Classified Myeloid Neoplasm	Myeloid Neoplasm Mutation(s)
1	ECD	<i>BRAF</i> V600E	MPN/MDS	<i>NRAS</i> G13D <i>ASXL1</i> Q733X
2	LCH	<i>BRAF</i> V600E	MPN/MDS	<i>TET2</i> X1268_Splice <i>KRAS</i> A146P
3	ECD	<i>BRAF</i> V600E	MPN	<i>JAK2</i> V617F <i>NRAS</i> G12S <i>TET2</i> L757fs*56 <i>U2AF1</i> Q157P
4	ECD	<i>BRAF</i> V600E	MPN/MDS	<i>ASXL1</i> Q733X <i>TET2</i> Q904X <i>TET2</i> Q321X <i>TET2</i> N1387S
5	ECD/LCH	<i>BRAF</i> V600E	MPN	<i>JAK2</i> V617F <i>TET2</i> K95X
6	ECD/LCH	<i>BRAF</i> V600E	MDS/AML	<i>IDH2</i> R140Q <i>TP53</i> N131K
7	ECD	<i>KRAS</i> G12S	None	Not Applicable
8	ECD	<i>BRAF</i> V600E	None	Not Applicable

Evaluation of Histiocytoses and Histiocytoses Plus Other Myeloid Neoplasm Co-occurrence via Patient-Derived Xenograft (PDX) Models

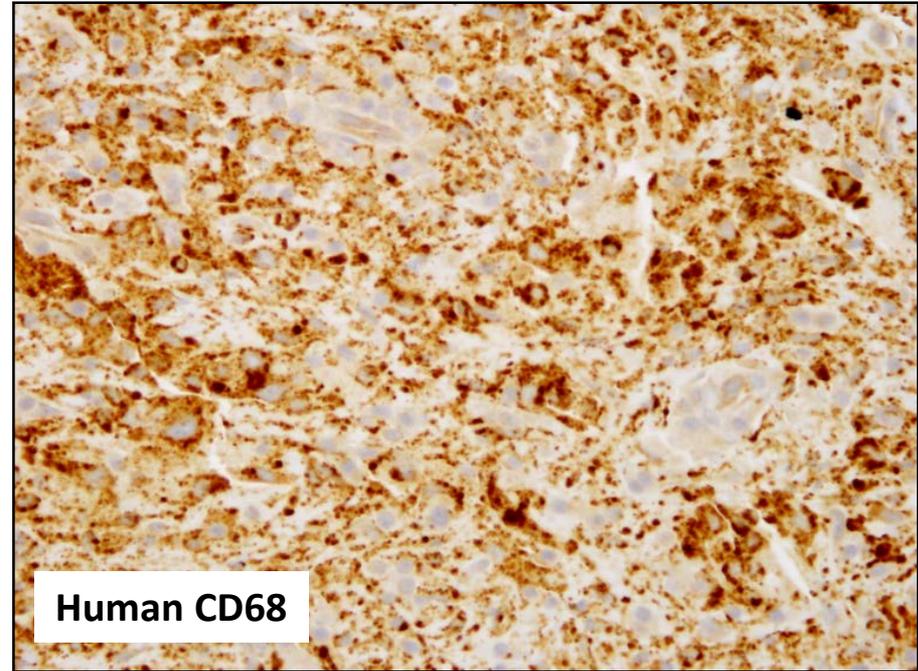


ECD Patient 7 Heart Biopsy with Non-Langerhans Cell Histiocytosis *KRAS* p.G12S

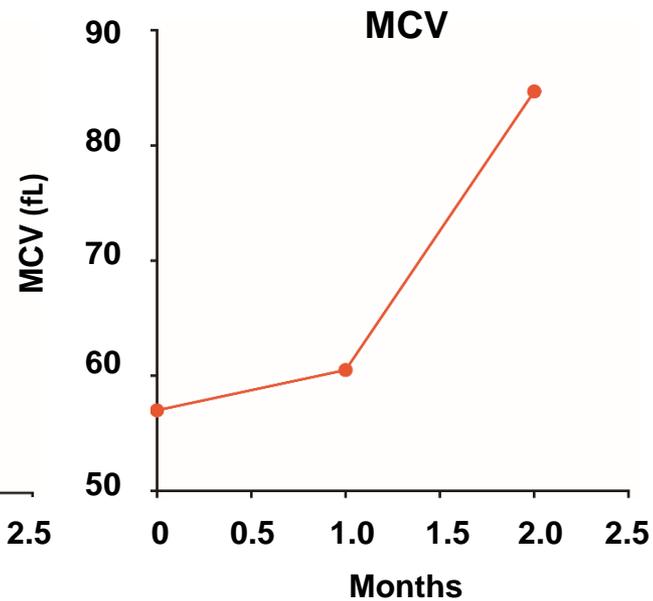
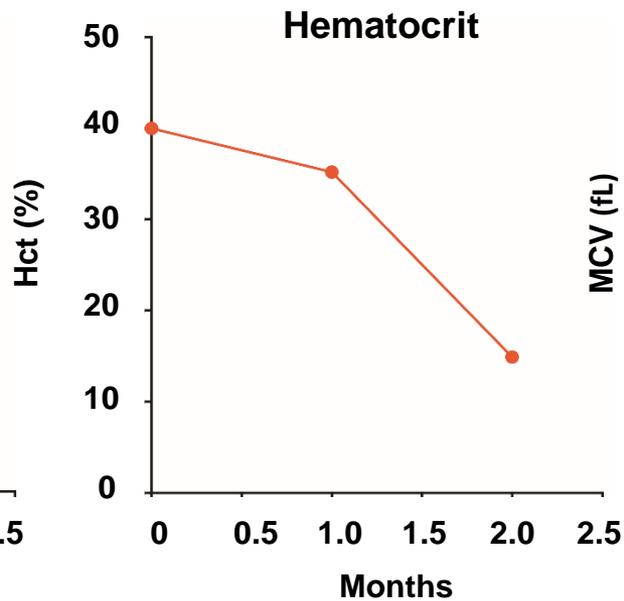
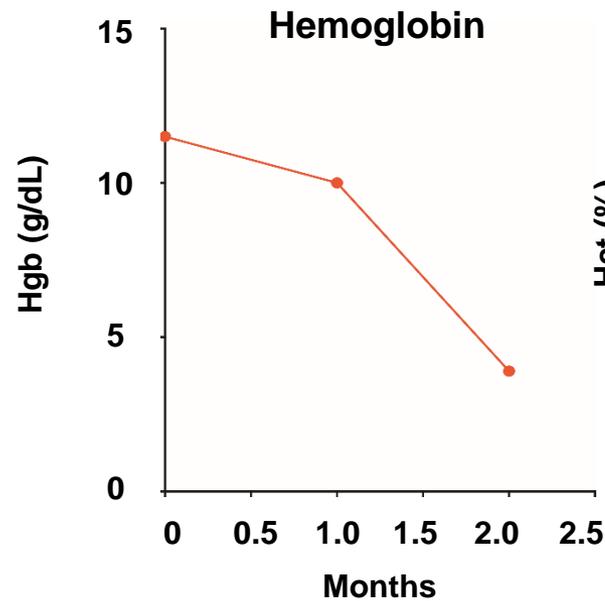
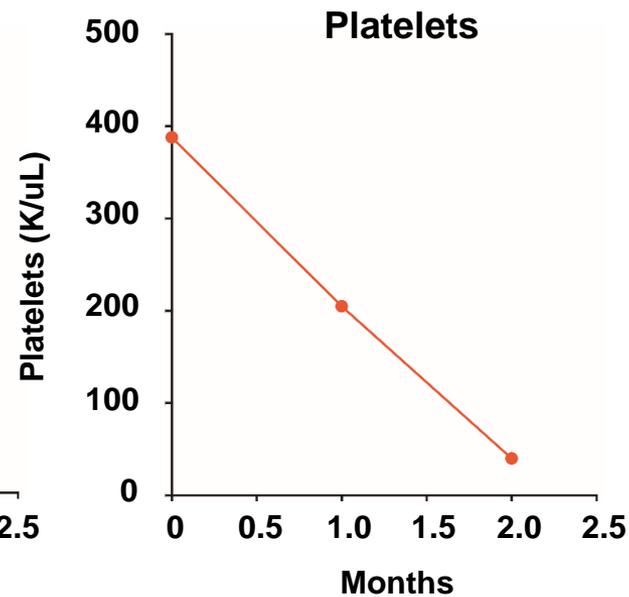
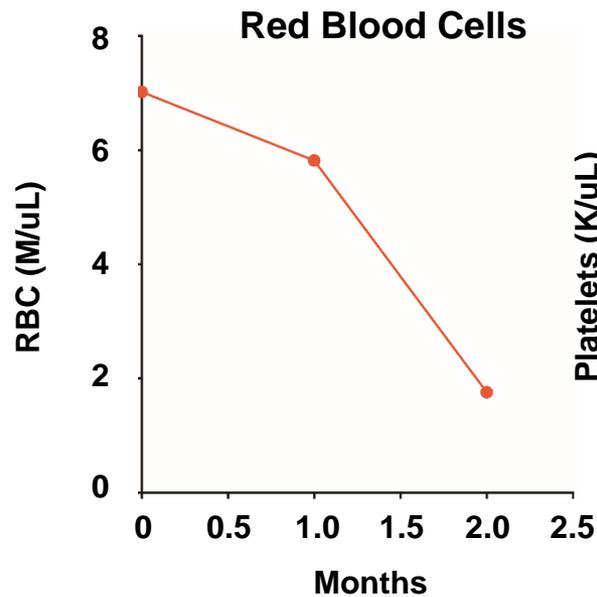
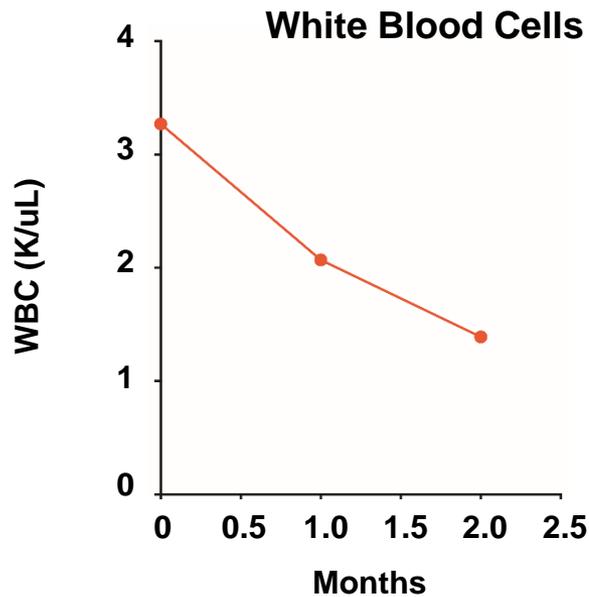
Patient 7 Heart Biopsy



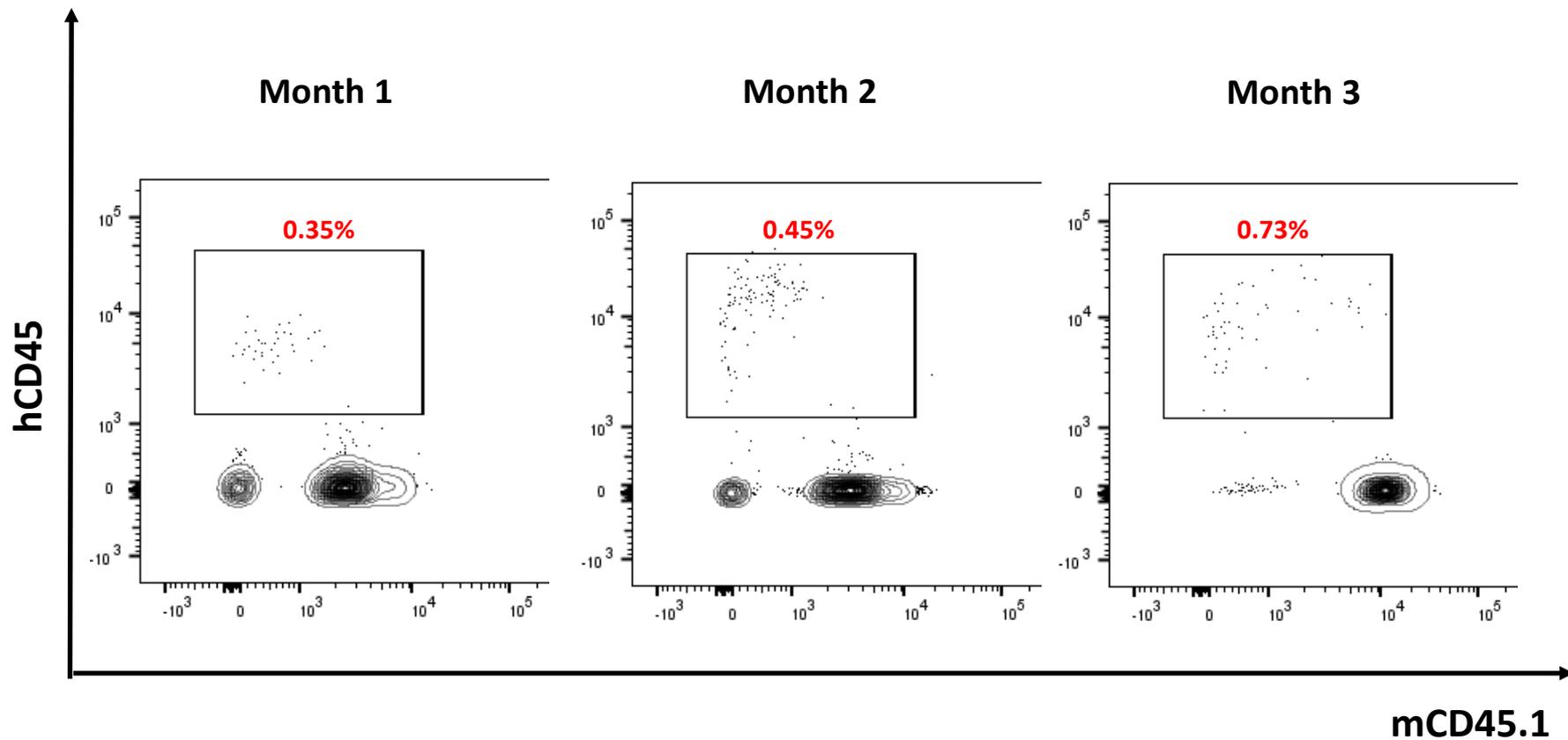
Patient 7 Heart Biopsy



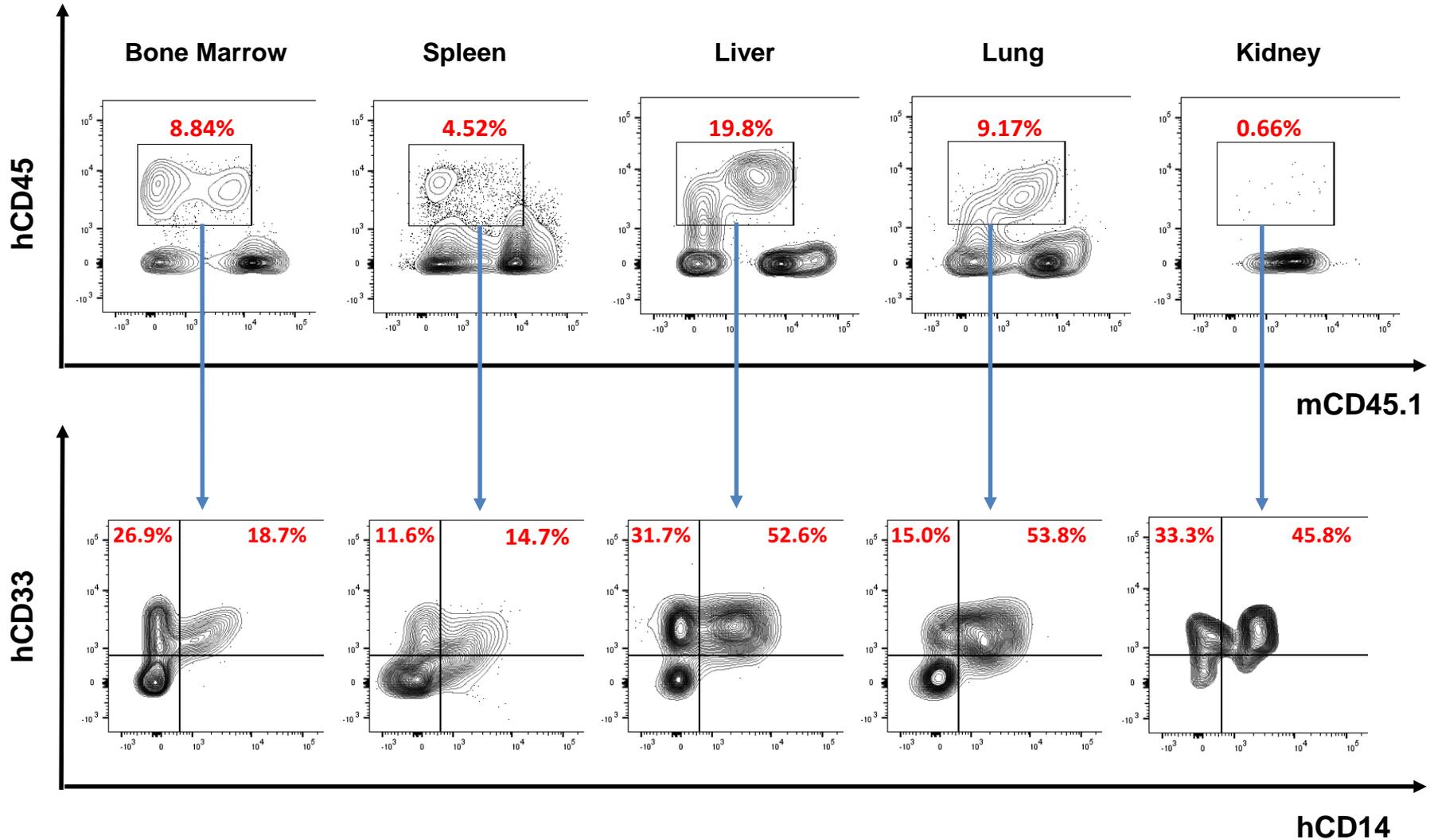
CBC Results for NSGS PDX Model from ECD Patient 7



Evidence of Engraftment of Human ECD Patient 7 hCD45+ Cells in NSGS PDX Model

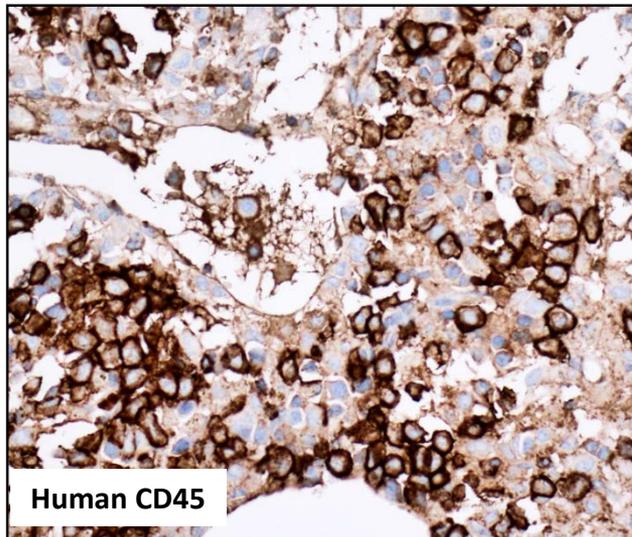
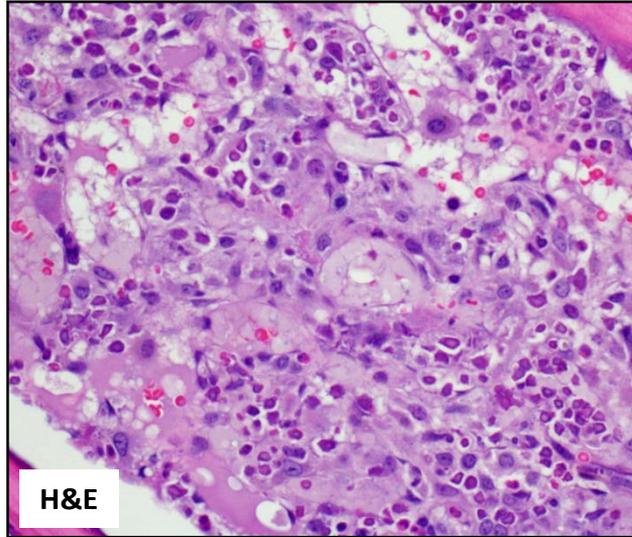


ECD Patient 7 PDX Model Tissue FACS Analysis

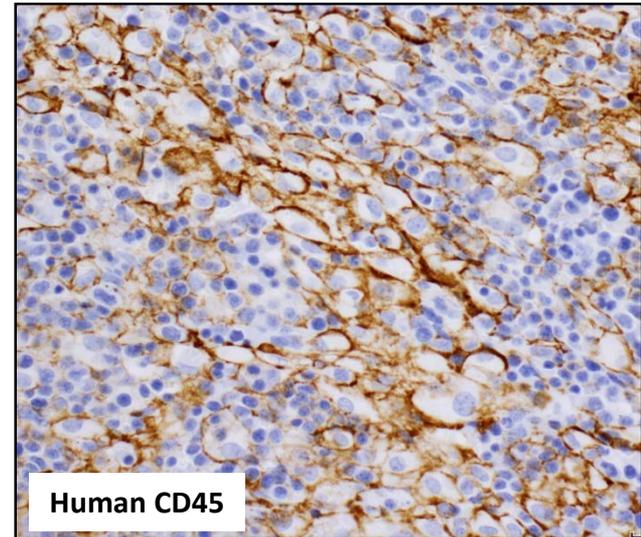
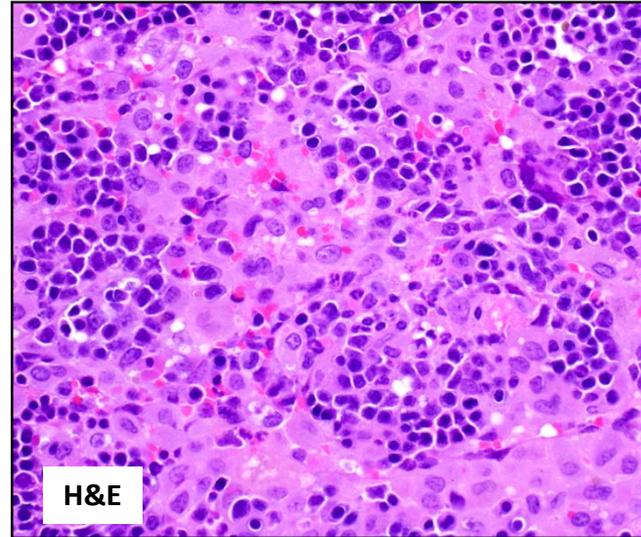


PDX Model Demonstrates Infiltration of Hematopoietic Tissues with Human CD45+ Foamy Histiocytes

PDX Bone Marrow

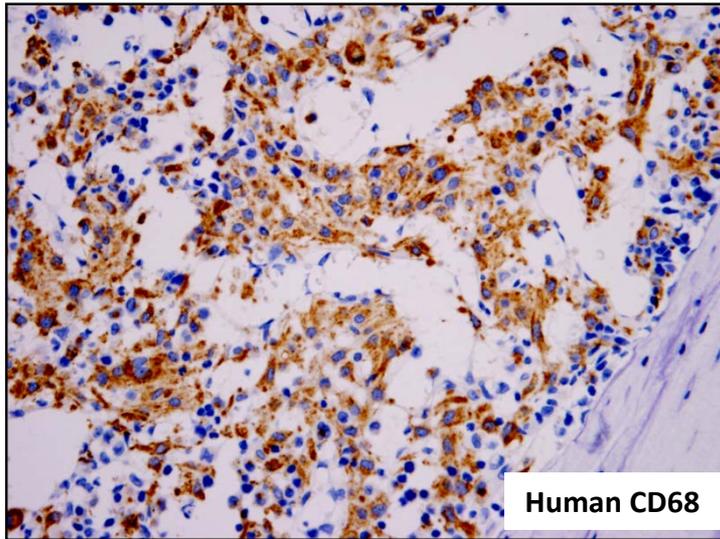


PDX Spleen

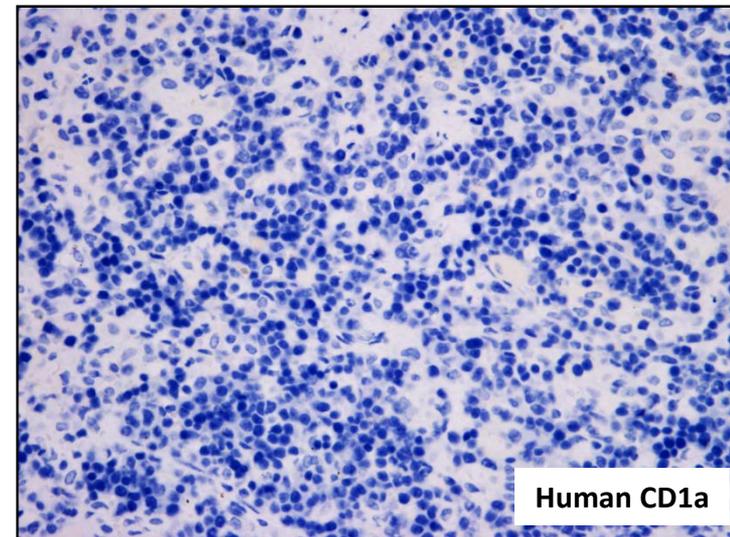
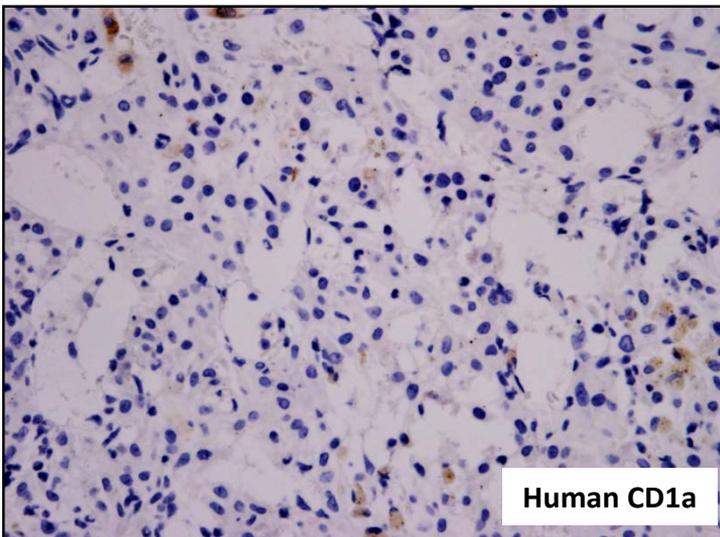
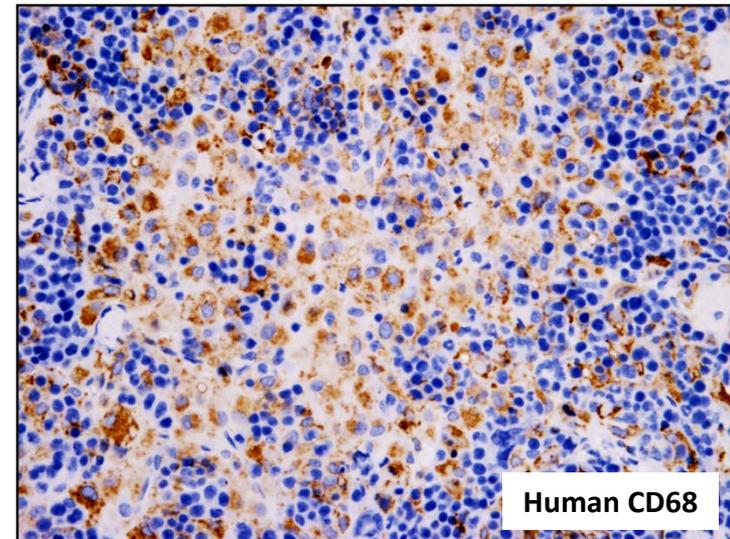


PDX Model Demonstrates Infiltration of Hematopoietic Tissues with Human CD68+ and CD1a- Foamy Histiocytes

PDX Bone Marrow

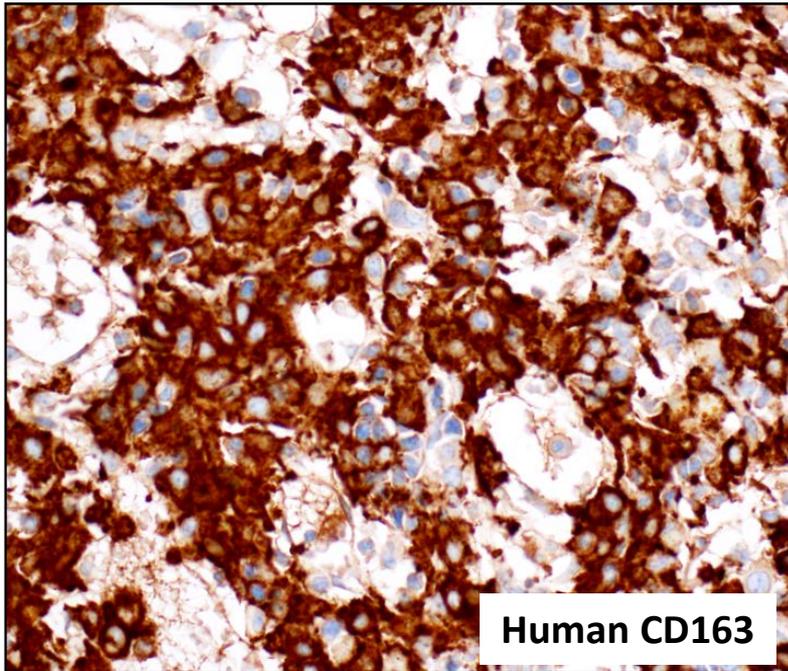


PDX Spleen

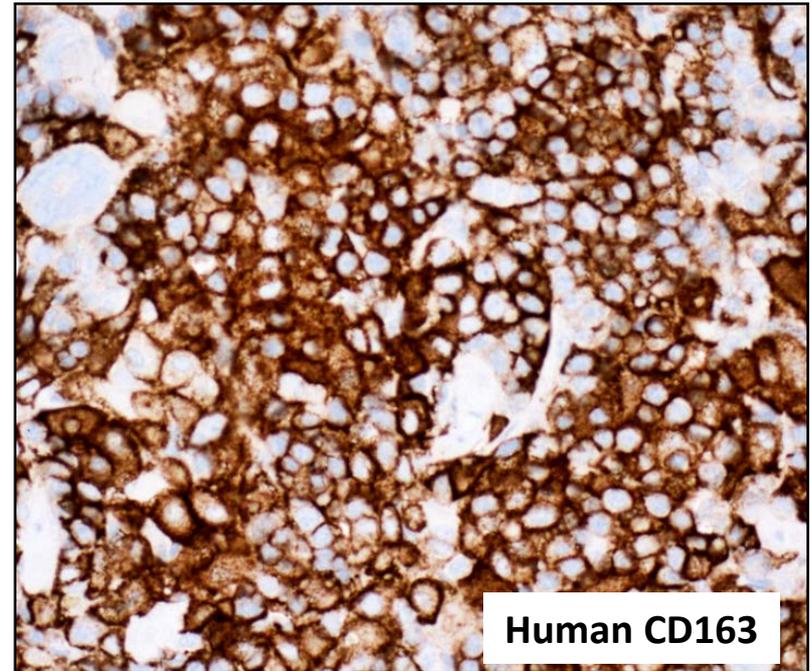


PDX Model Demonstrates Infiltration of Hematopoietic Tissues with Human CD163+ Foamy Histiocytes

PDX Bone Marrow

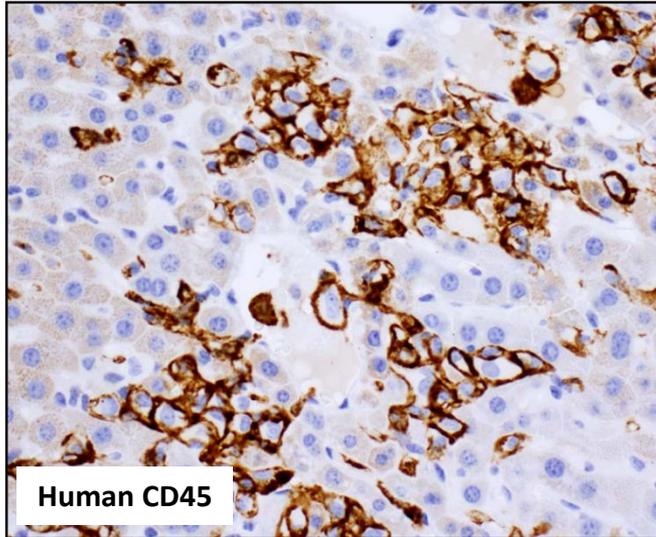


PDX Spleen

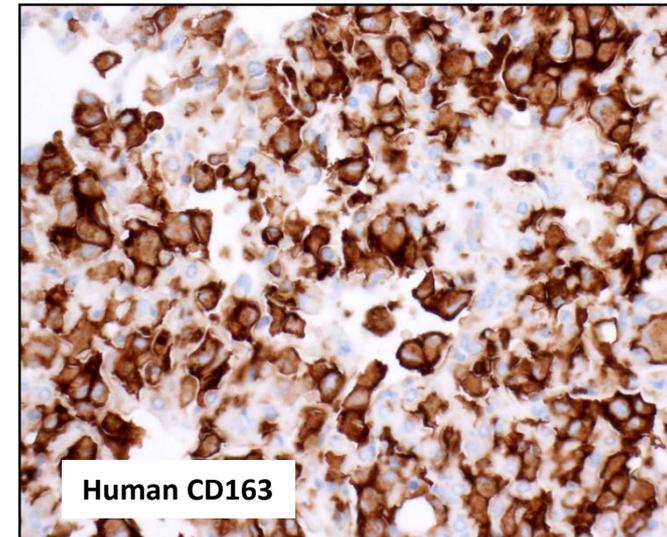
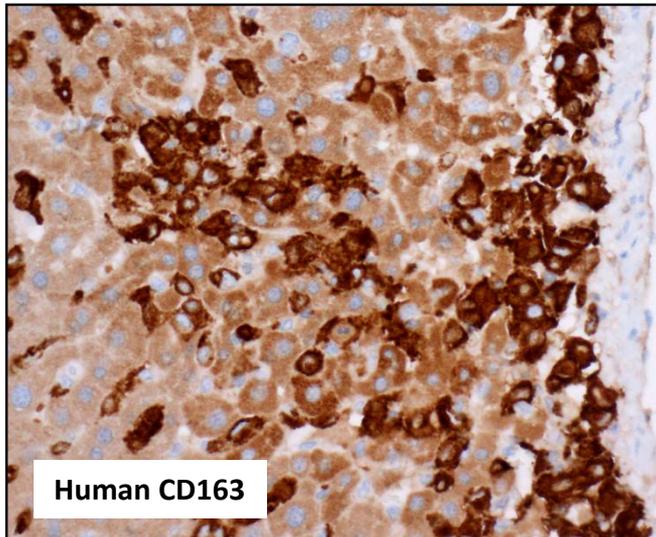
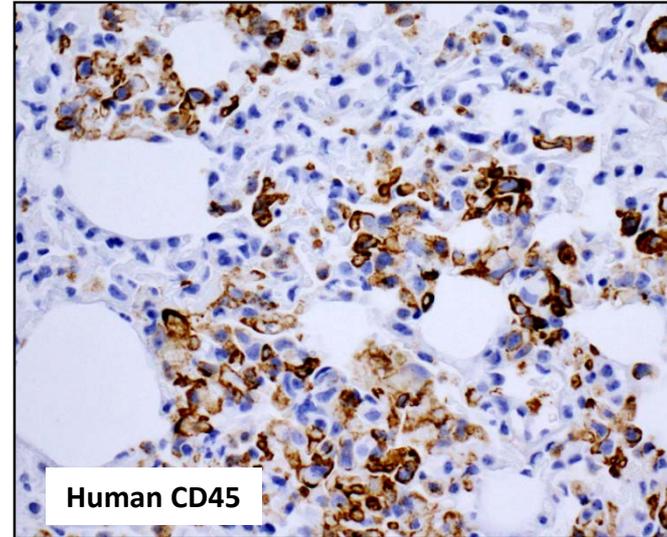


PDX Model Demonstrates Infiltration of Other Tissues with Human CD45+ and CD163+ Foamy Histiocytes

PDX Liver



PDX Lung

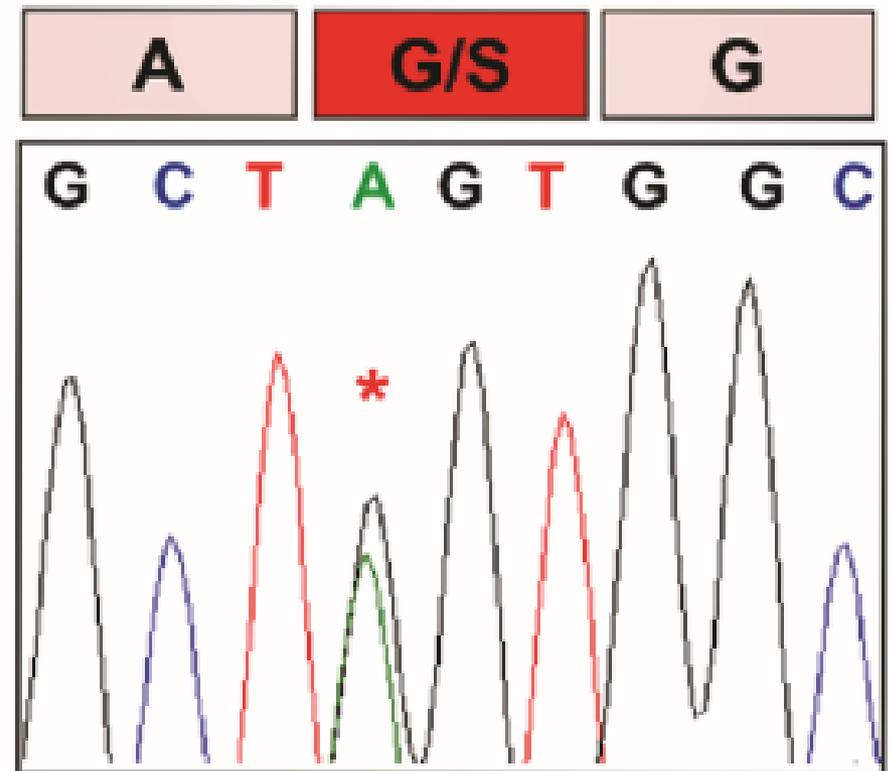
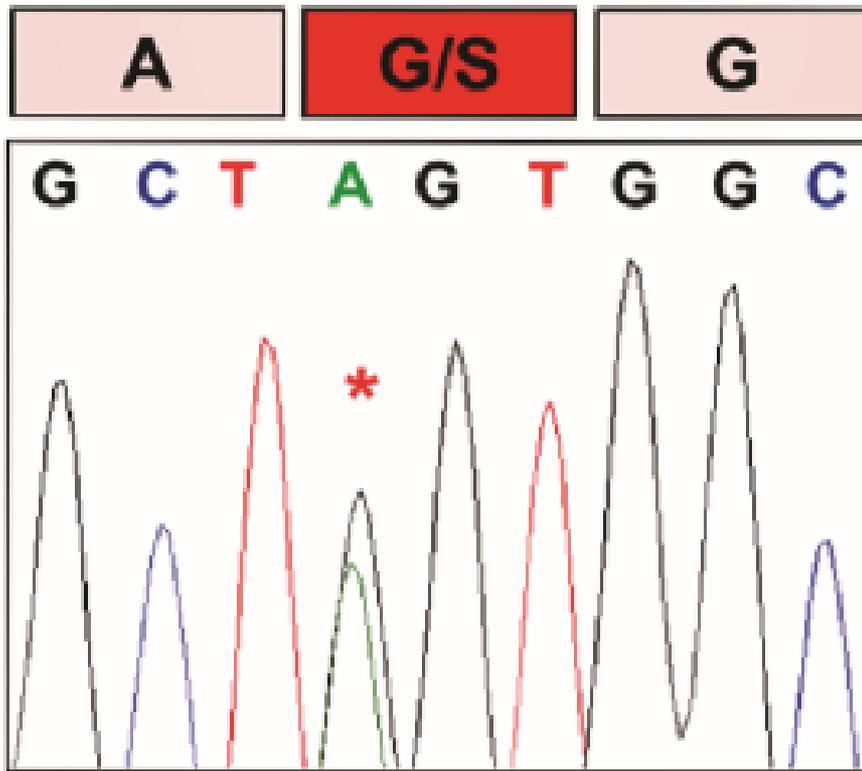


PDX Model Demonstrates Patient 7

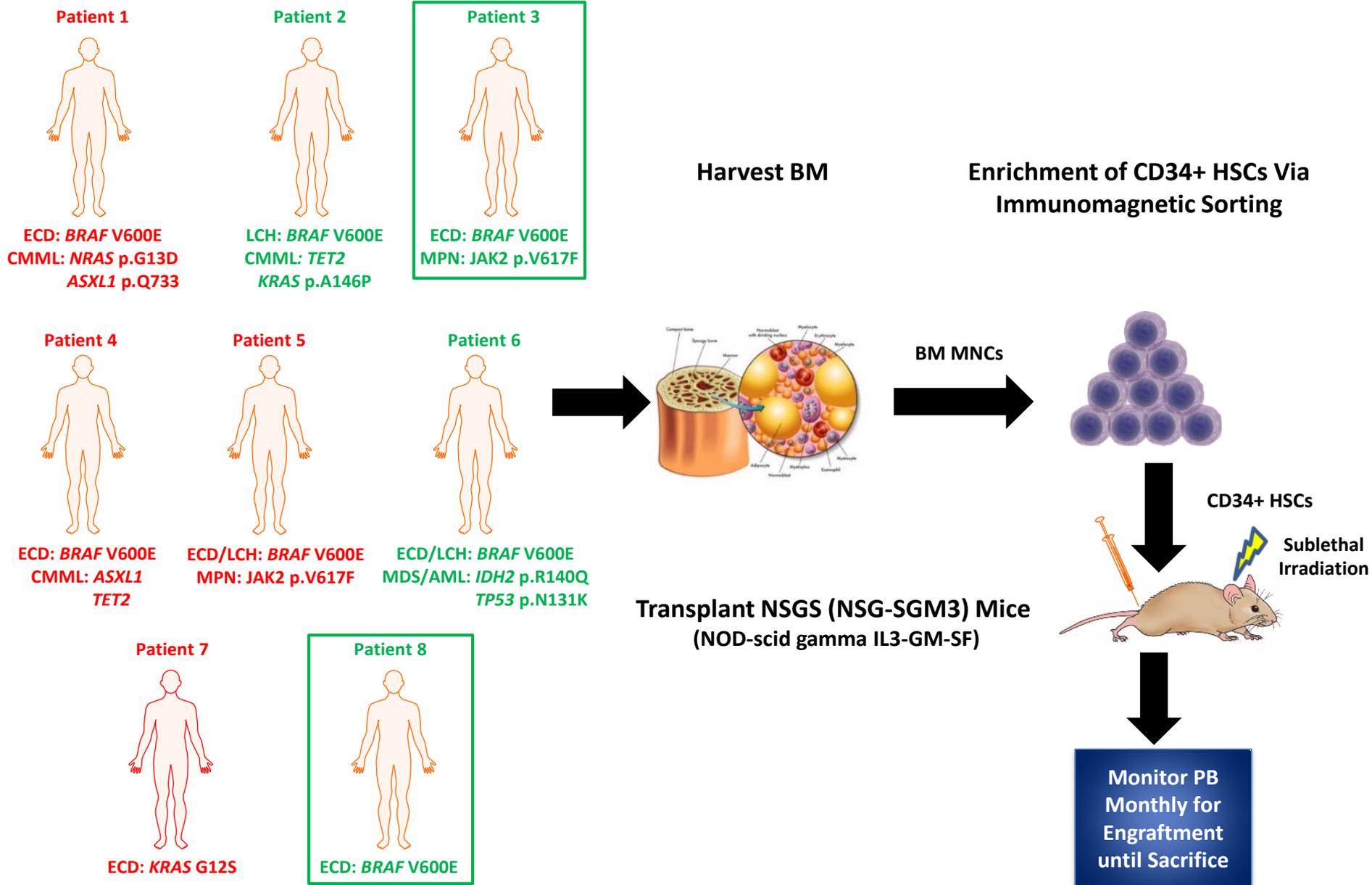
KRAS c.34G>A; p.G12S

PDX Bone Marrow

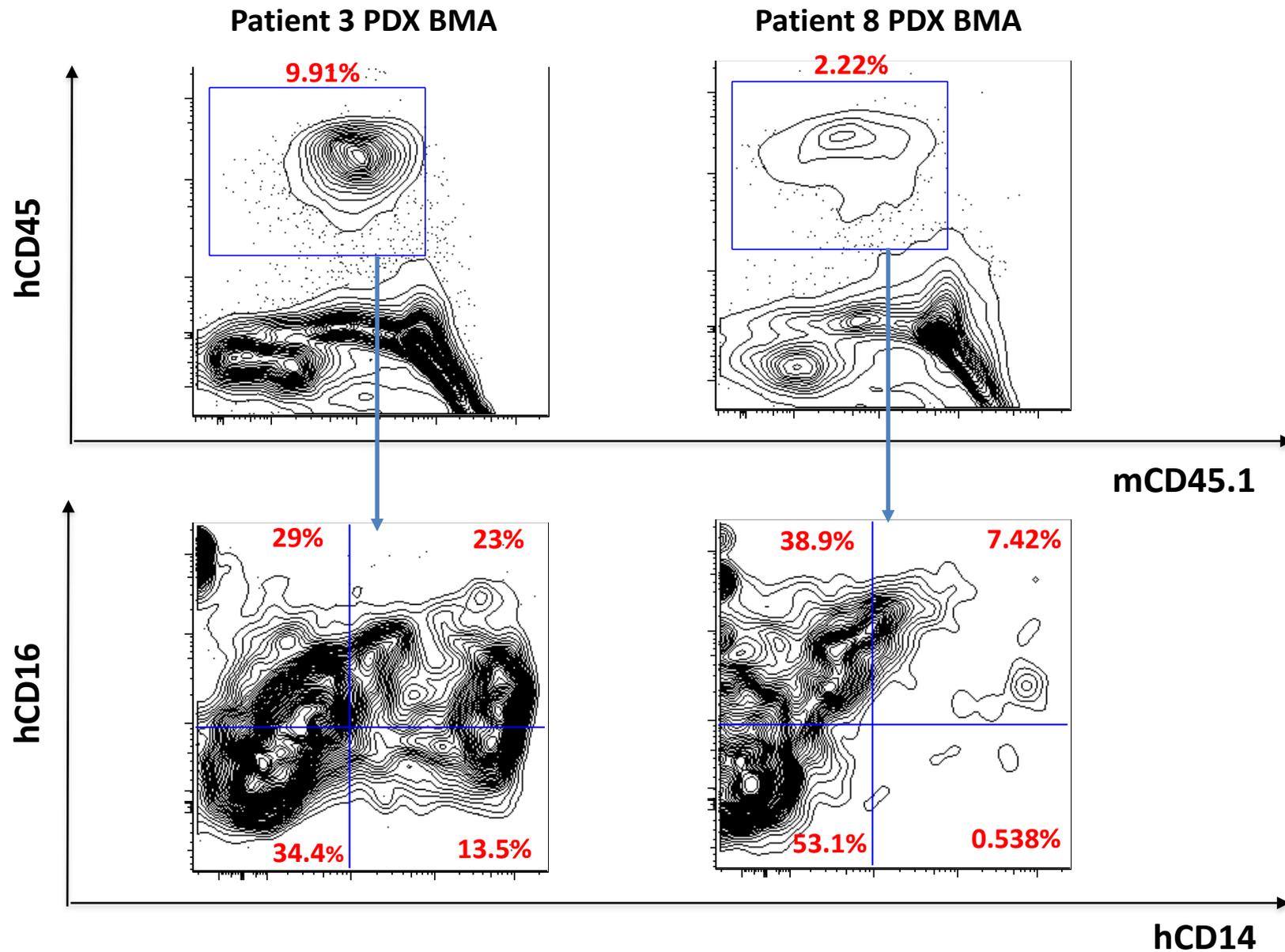
PDX Spleen



Evaluation of Histiocytoses and Histiocytoses Plus Other Myeloid Neoplasm Co-occurrence via Patient-Derived Xenograft (PDX) Models



Additional Evidence of Engraftment of Patient 3 and Patient 8 hCD45+ Cells in NSGS PDX Models



Conclusions and Future Directions

- **Functional evidence that the CD34+ compartment can initiate histiocytosis**
- **Current studies involve adult histiocytic disorders only, but pediatric histiocytoses may have a different cell of origin**
- **Further work is needed to determine the frequency of successful engraftment of CD34+ cells in histiocytoses**
 - **Based on current experience the engraftment rate is 1/8**
- **Further PDX murine model characterization underway**
 - Continuing to monitor surviving ECD (2), ECD/LCH (1), LCH (1) PDX models for engraftment
 - Serial transplantation ongoing using hCD34+ cells from engrafted NSGS PDX murine models
 - Monitoring NSGS mice recently transplanted with normal human CD34+ cord blood
- **Interrogation of different purified cell subsets from systemic histiocytoses patients is needed to refine the cell(s)-of-origin of the systemic histiocytoses**

THANK YOU

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