

Multidimensional Characterization of Tumor–Immune Architecture Reveals Clinically Relevant Classic Hodgkin Lymphoma Subtypes

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Medicine
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UHN

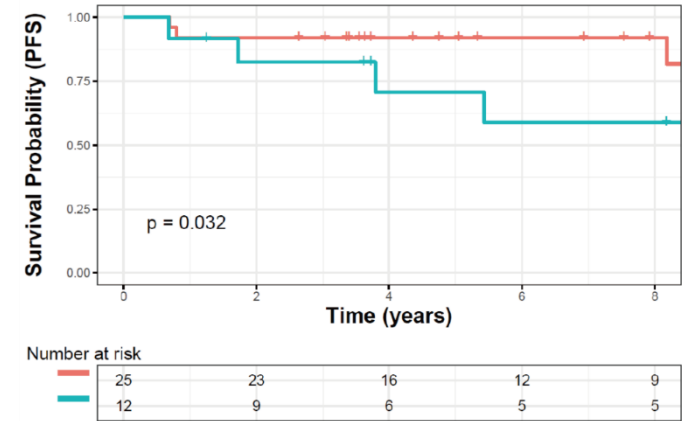
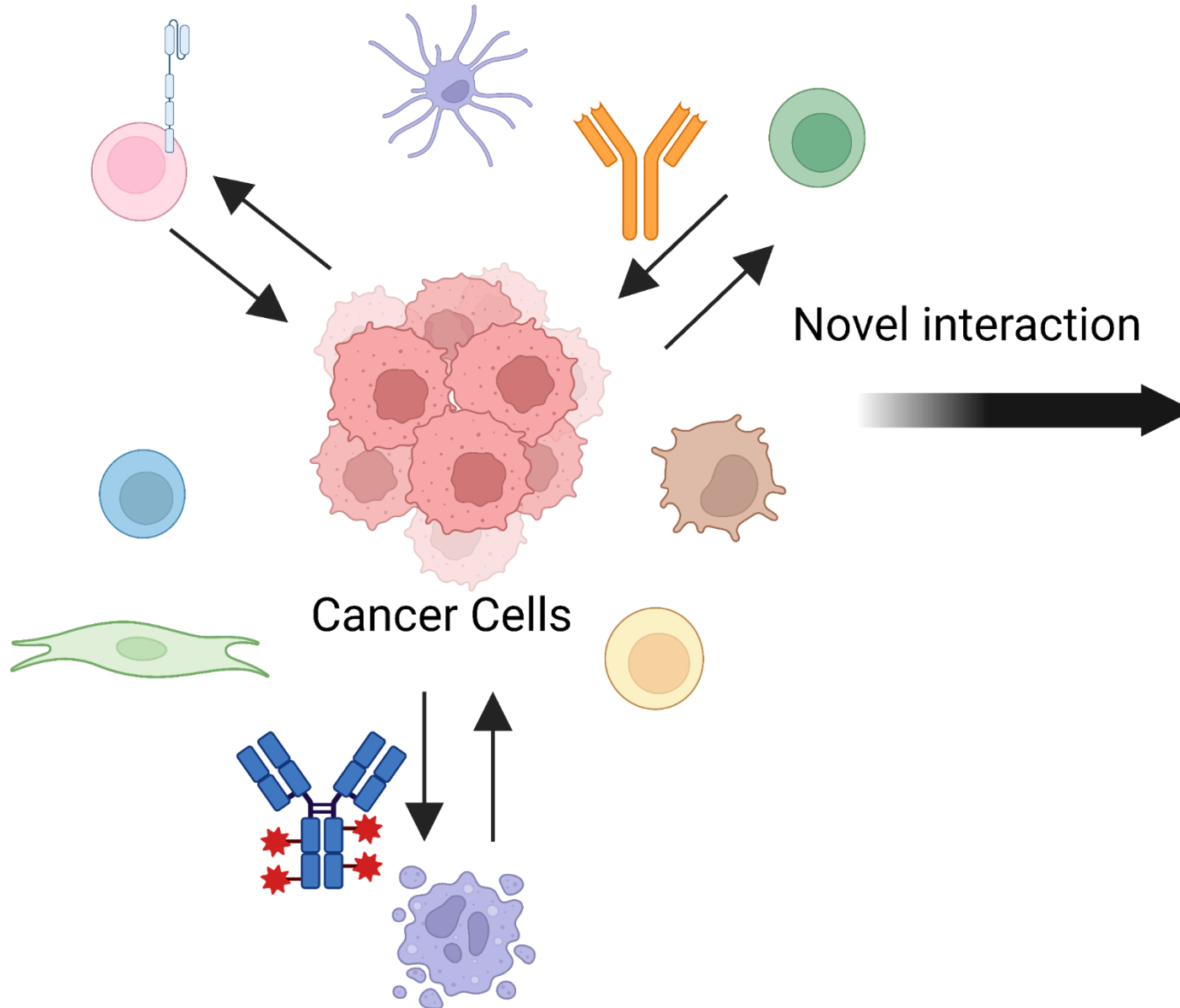
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Conflict of interest statement

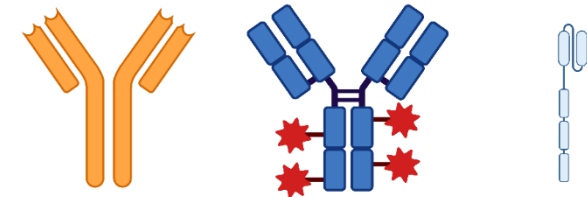
My personal disclosures are regarding:

Author	
Employment, leadership position	NA
Consulting / expert review activities	Kyowa Kirin
Ownership of shares or funds	NA
Patent, copyright, sales license	NA
Honorarium / fee	Chugai Pharma
Financing of scientific studies	NA
Other financial relations	NA
Intangible conflicts of interest	NA

Translational Research

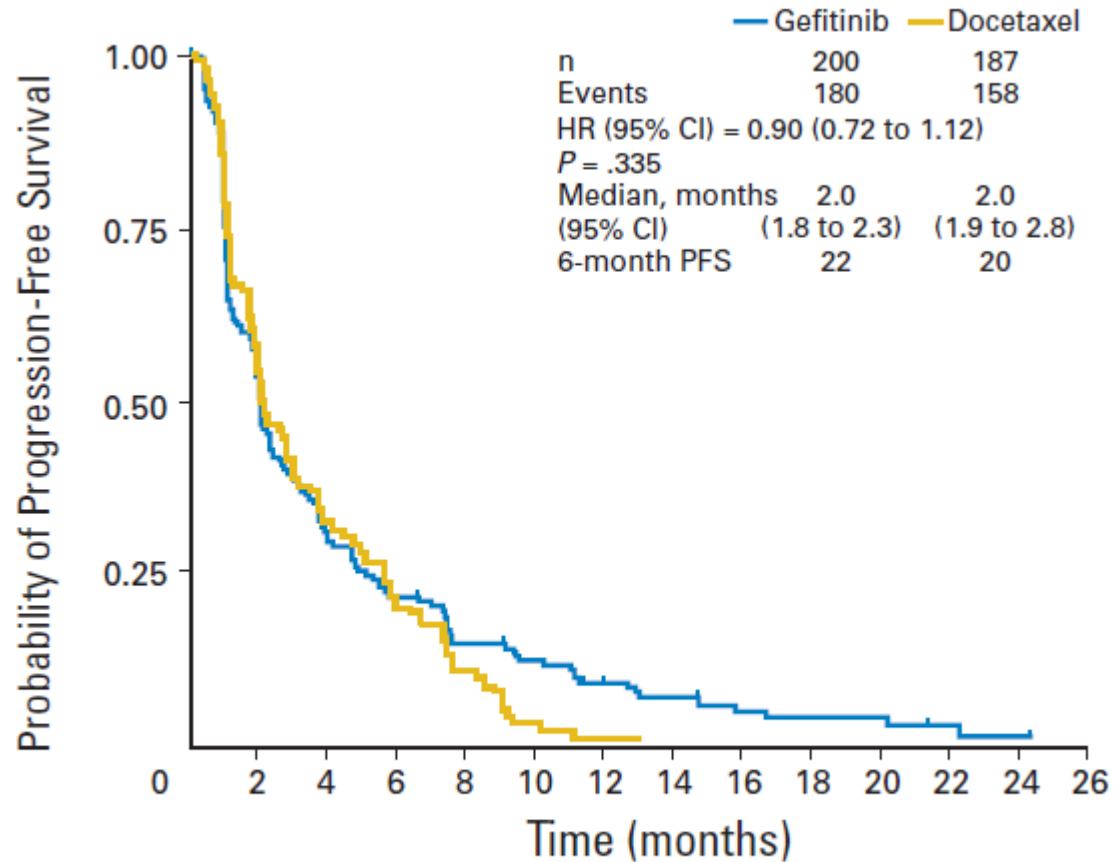


Novel biomarker

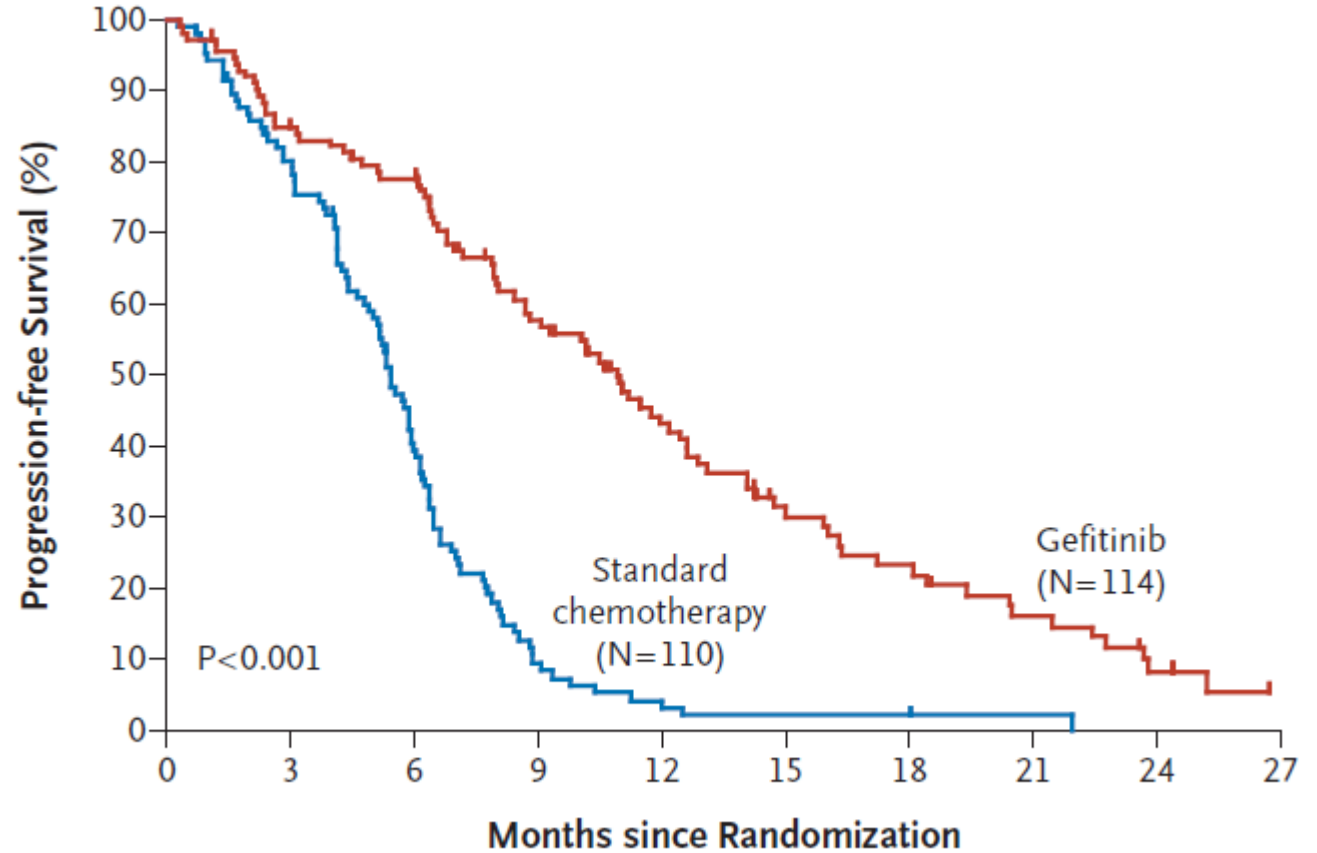


Novel treatment

Biomarker transformed treatment landscape



Patients at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Gefitinib	200	95	55	39	26	20	13	9	5	4	4	2	1	0
Docetaxel	187	86	45	25	13	3	1	0	0	0	0	0	0	0



Discovery of EGFR mutation

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EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

[J. GUILLERMO PAEZ](#), [PASI A. JÄNNE](#), [JEFFREY C. LEE](#), [SEAN TRACY](#), [HEIDI GREULICH](#), [STACEY GABRIEL](#), [PAULA HERMAN](#), [FREDERIC J. KAYE](#), [NEAL LINDEMAN](#), [...]

[MATTHEW MEYERSON](#)

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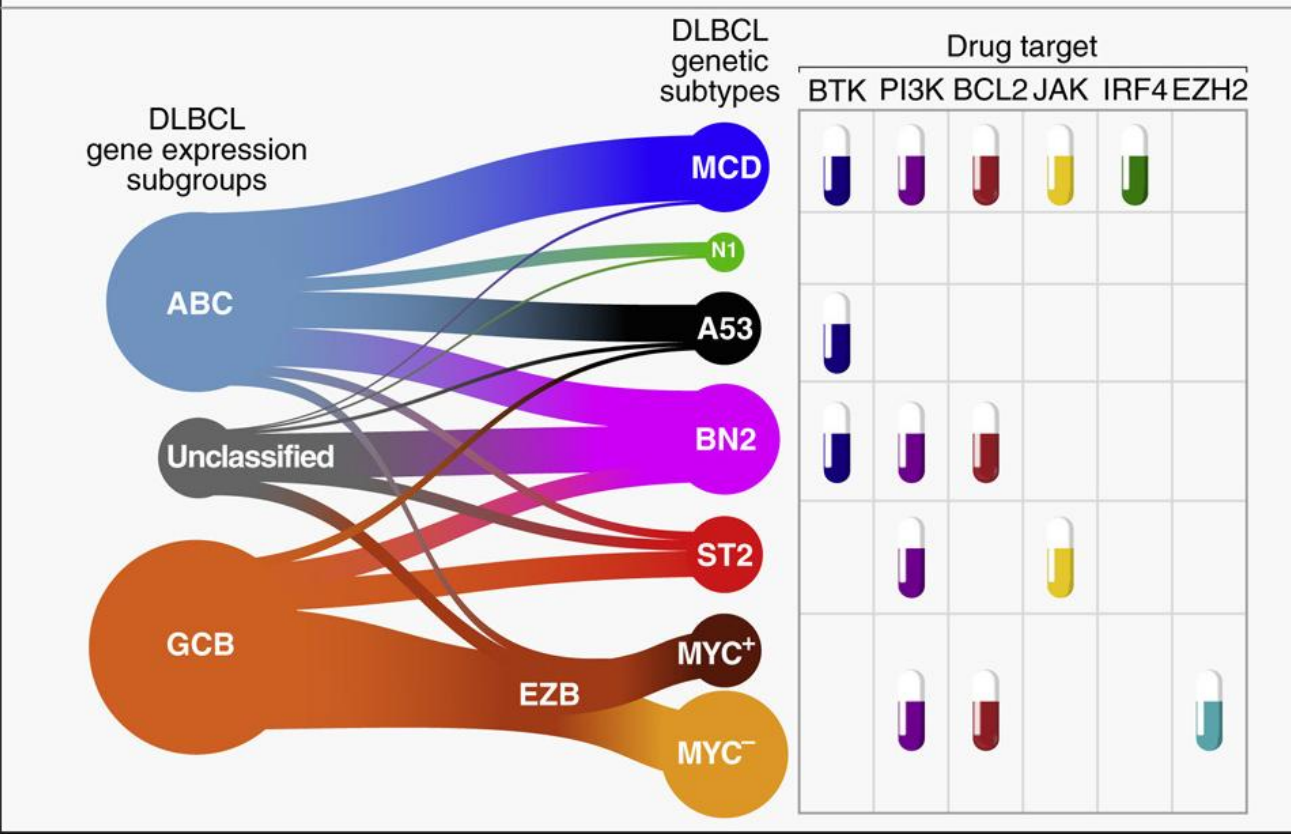
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EGFR mutation

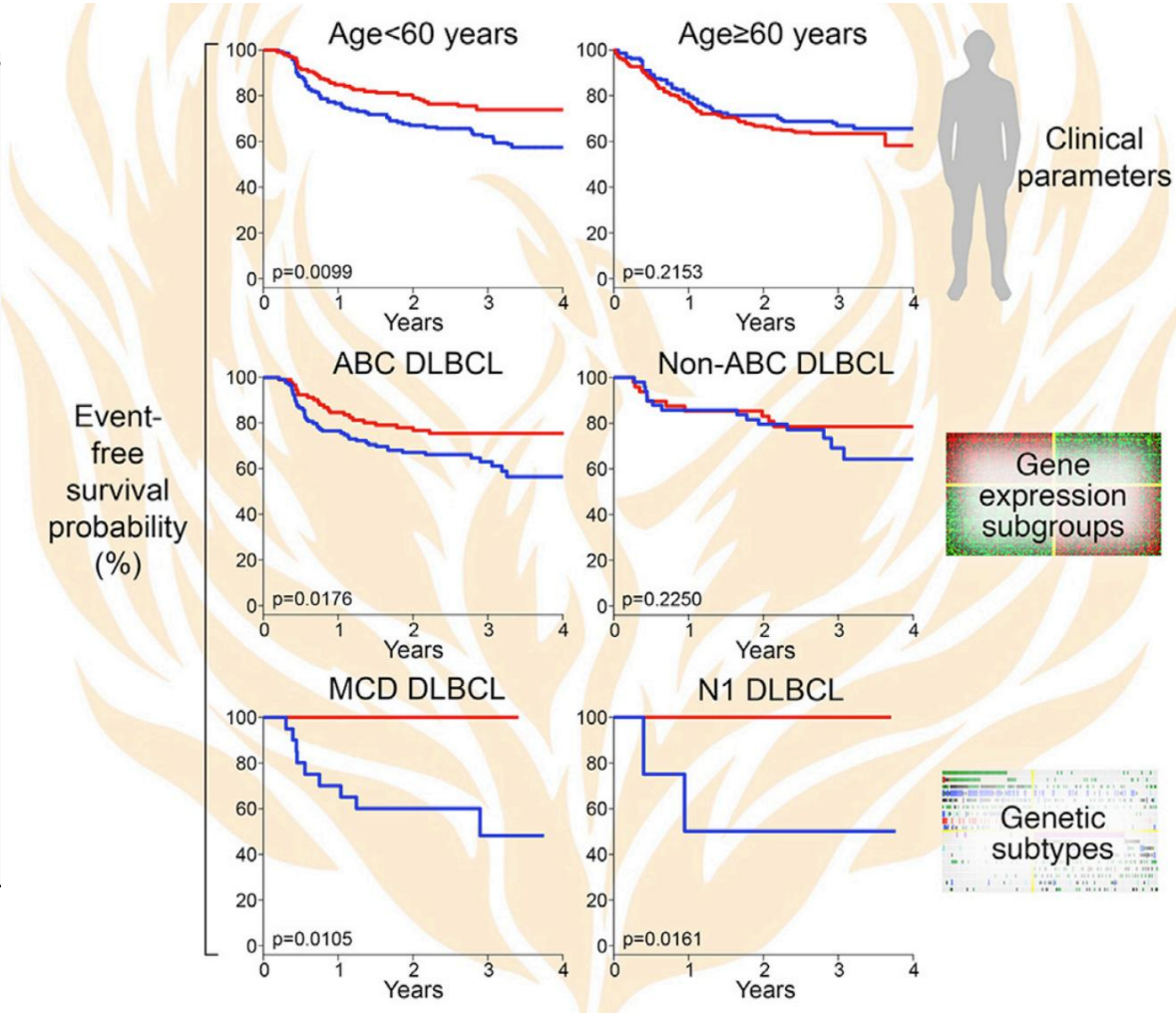


EGFR TKI

Can new genetic classification lead to improved therapeutic targeting in lymphoma?



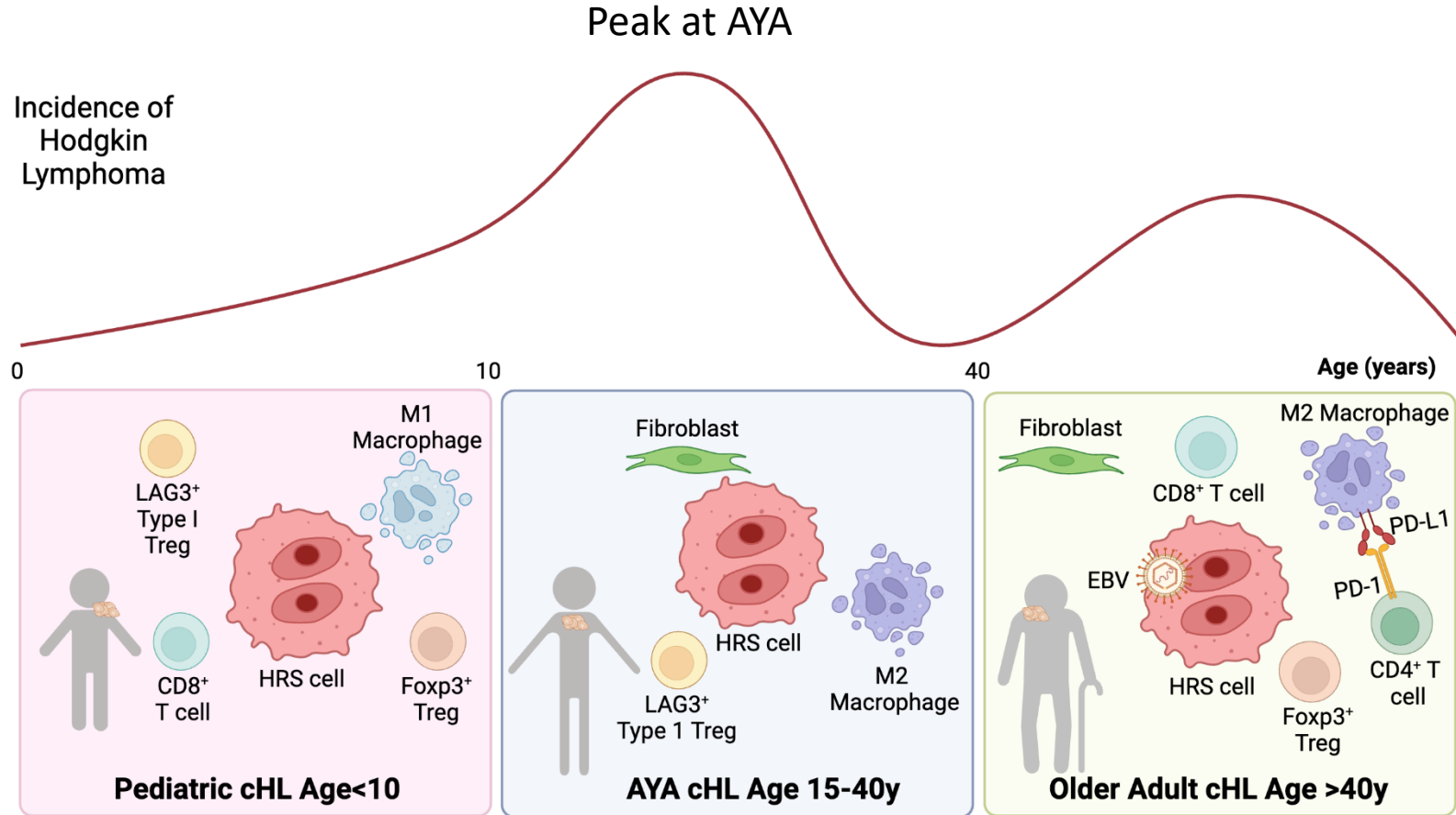
Wright, Cancer Cell 2020



Ibrutinib + R-CHOP in diffuse large B cell lymphoma

Wilson et al., Cancer Cell, 2021

Classic Hodgkin lymphoma (cHL) :An ideal disease context for dose de-escalation and escalation strategies.



Young Age Predominant

- High efficacy
- Minimum toxicity

Success with response adopted Treatment with PET/CT

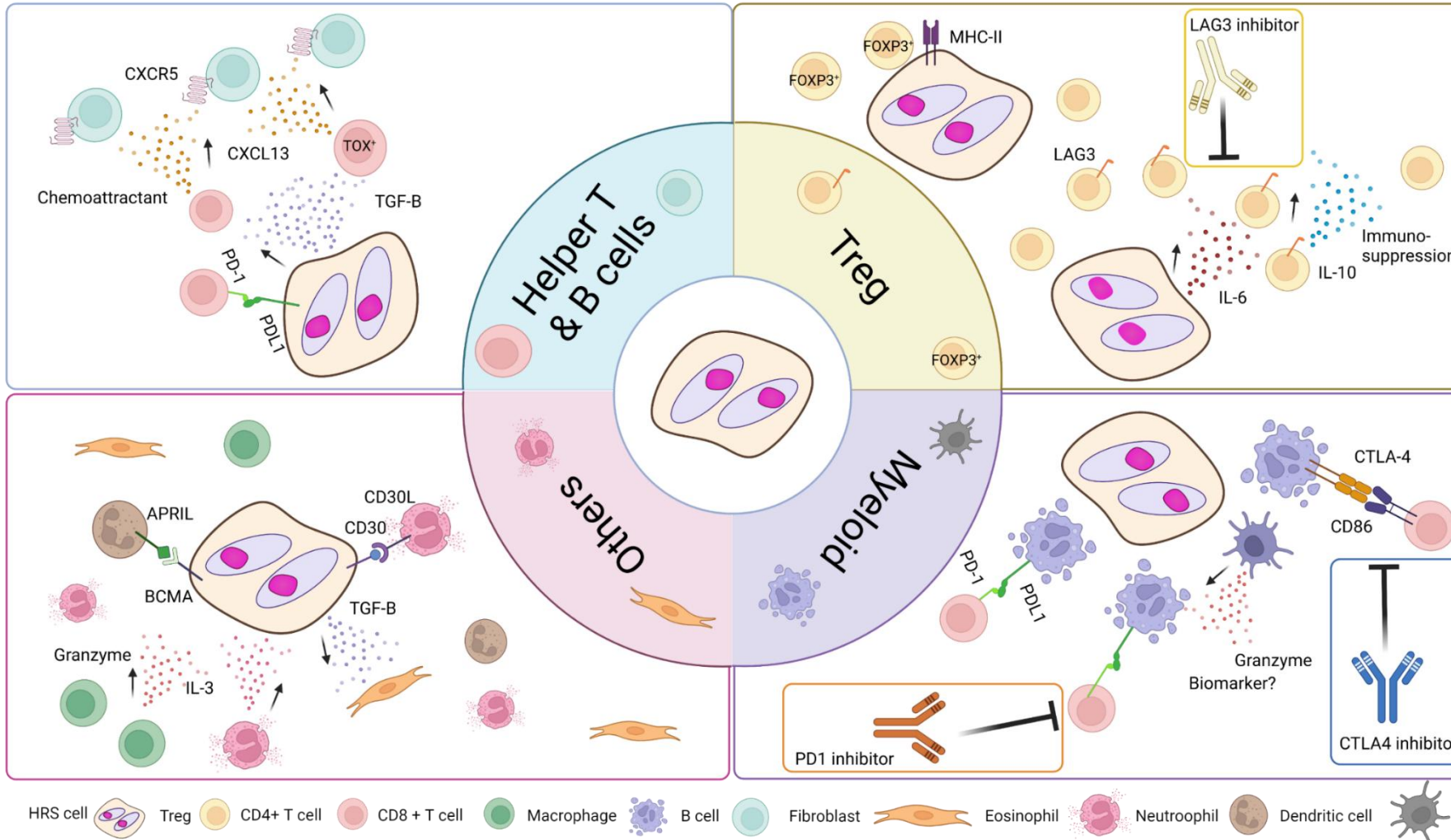
- Interim PET

Treatment options

- Various chemo
- Auto-SCT
- Targeted (e.g. CD30)
- Immuno-therapy (PD-1)

Heterogeneous biology

Rare (~1%) HRS cell populations hampered genomic study for HRS cells in Hodgkin lymphoma (HL)

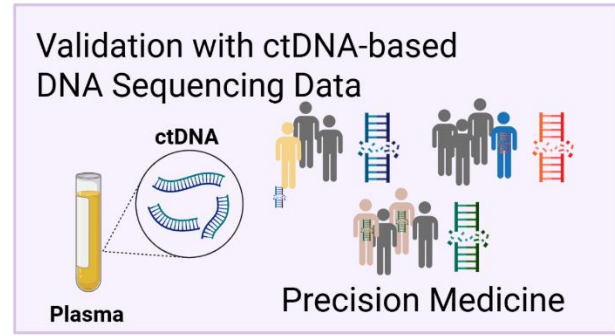
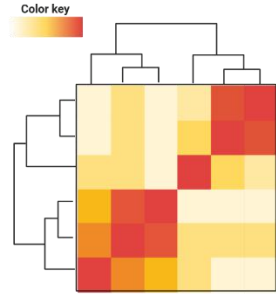
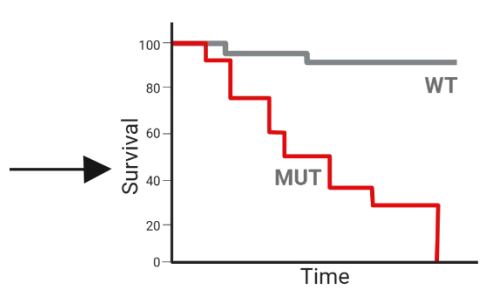
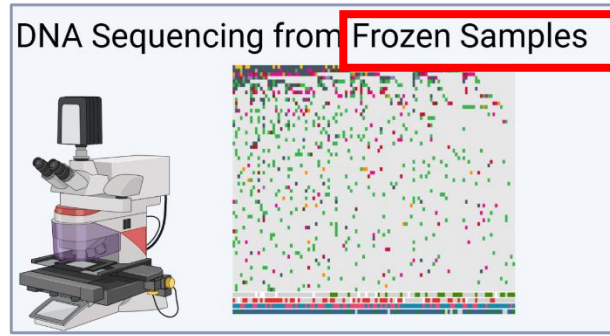


Only limited preliminary data exist that link HRS cell genomics with the unique composition and functional state of the microenvironment and targetable biology


Multidimensional characterization of cellular ecosystems in HL

Aim: Determine the biology that underlies molecular heterogeneity

Develop Publicly available tool: HLGen



Discovery Cohort (n = 114)



Standard Chemotherapy in Population-based Cohort

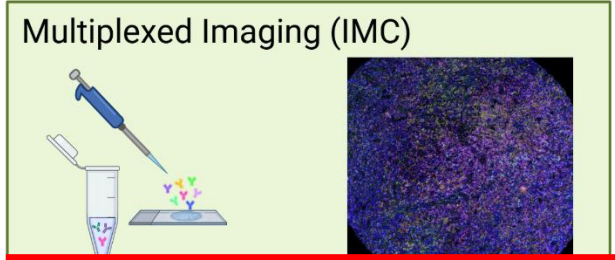
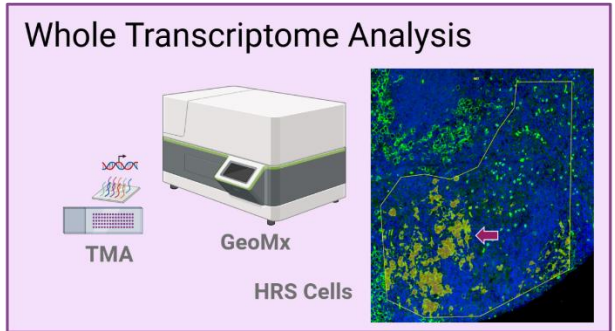

Clinical Features/
Outcome Correlation

NMF Clustering:
Molecular Subtype

Independent Validation Cohort (n = 293)

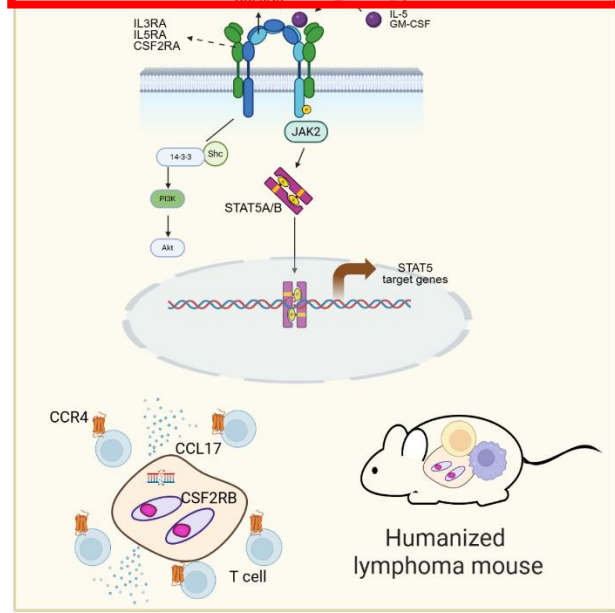


Tissue Microarray (TMA)
Construction

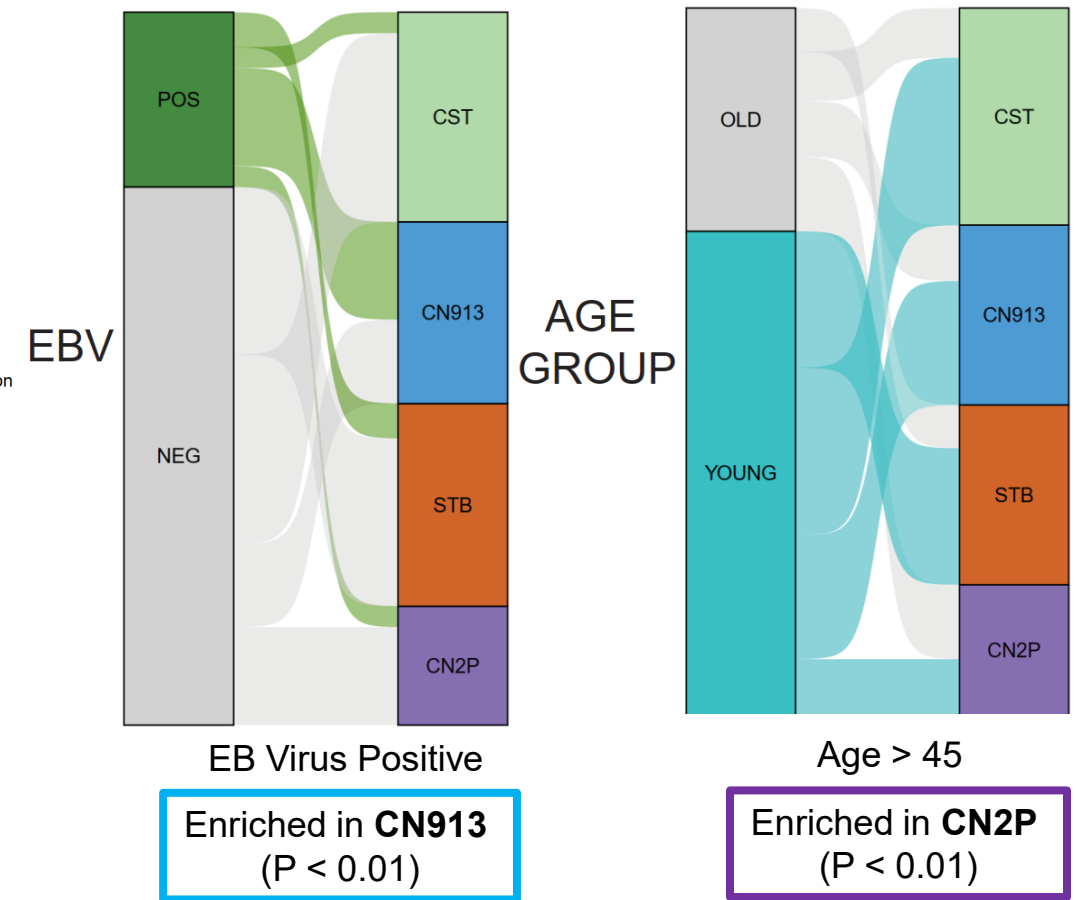
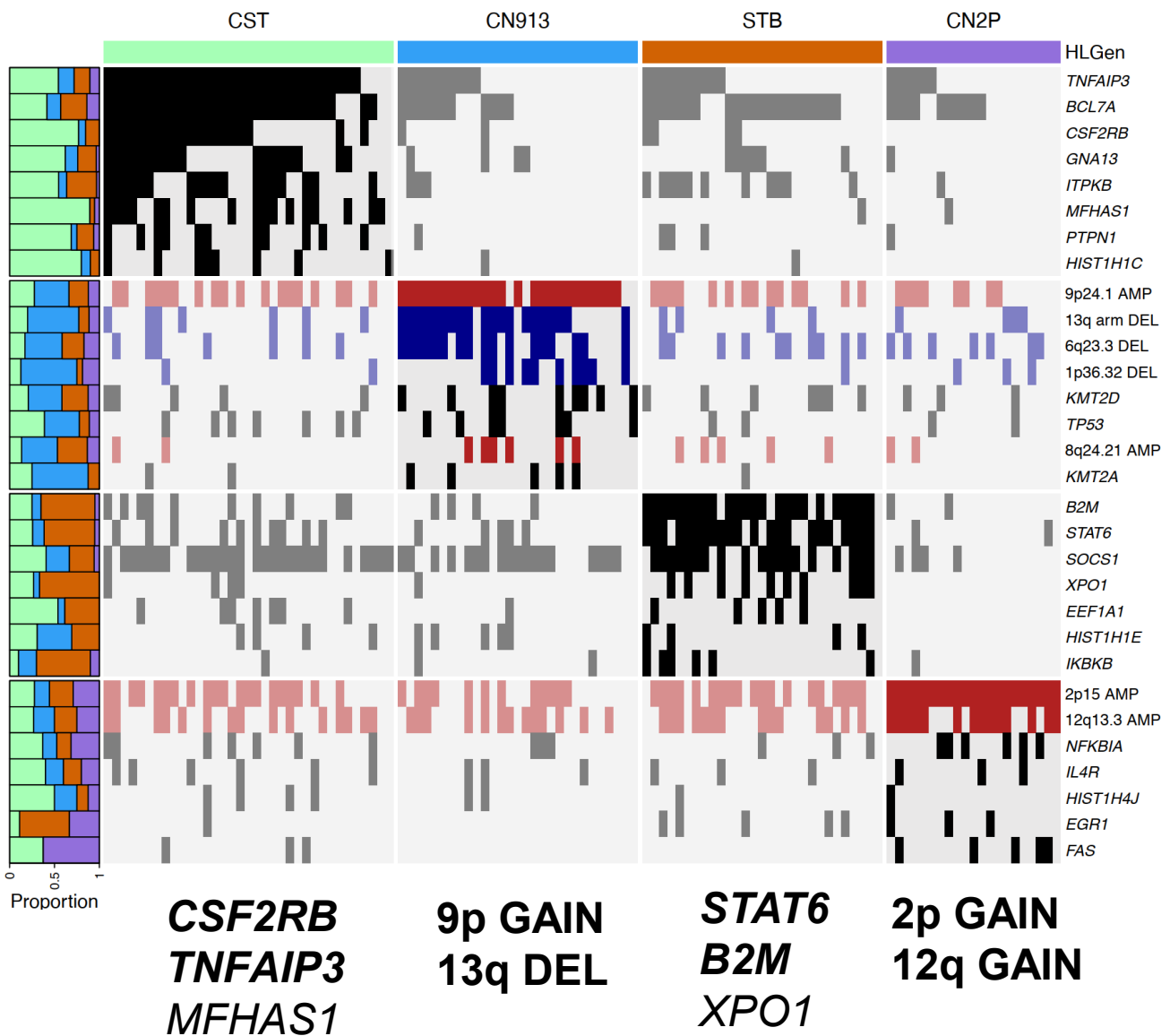


Tumor Microenvironment Correlation

Functional modeling of CST subtype

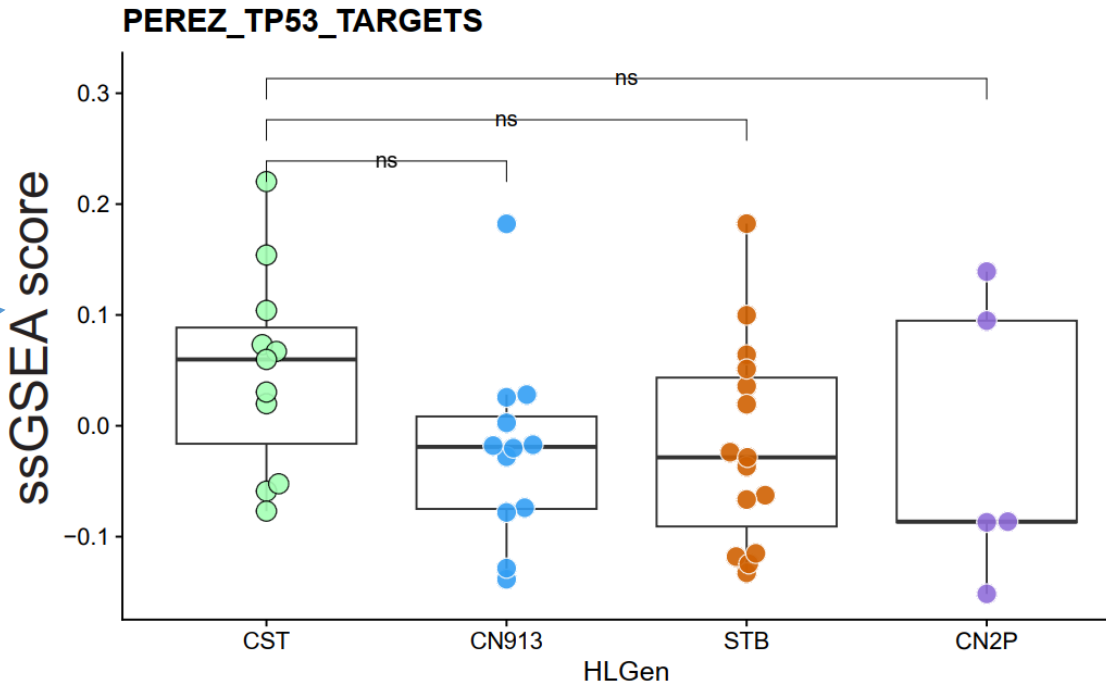
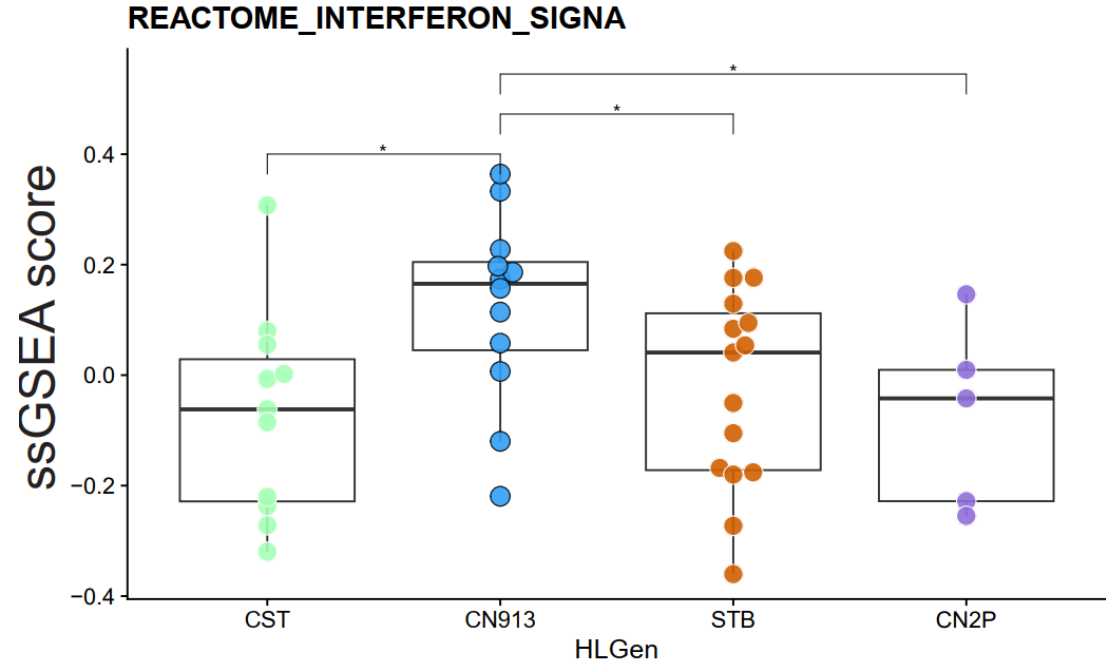
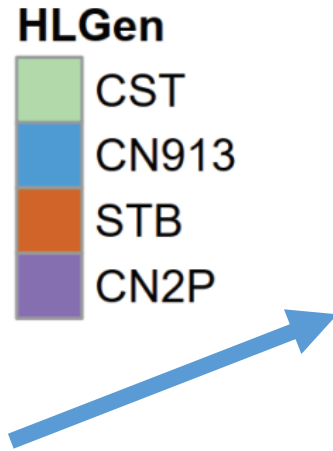
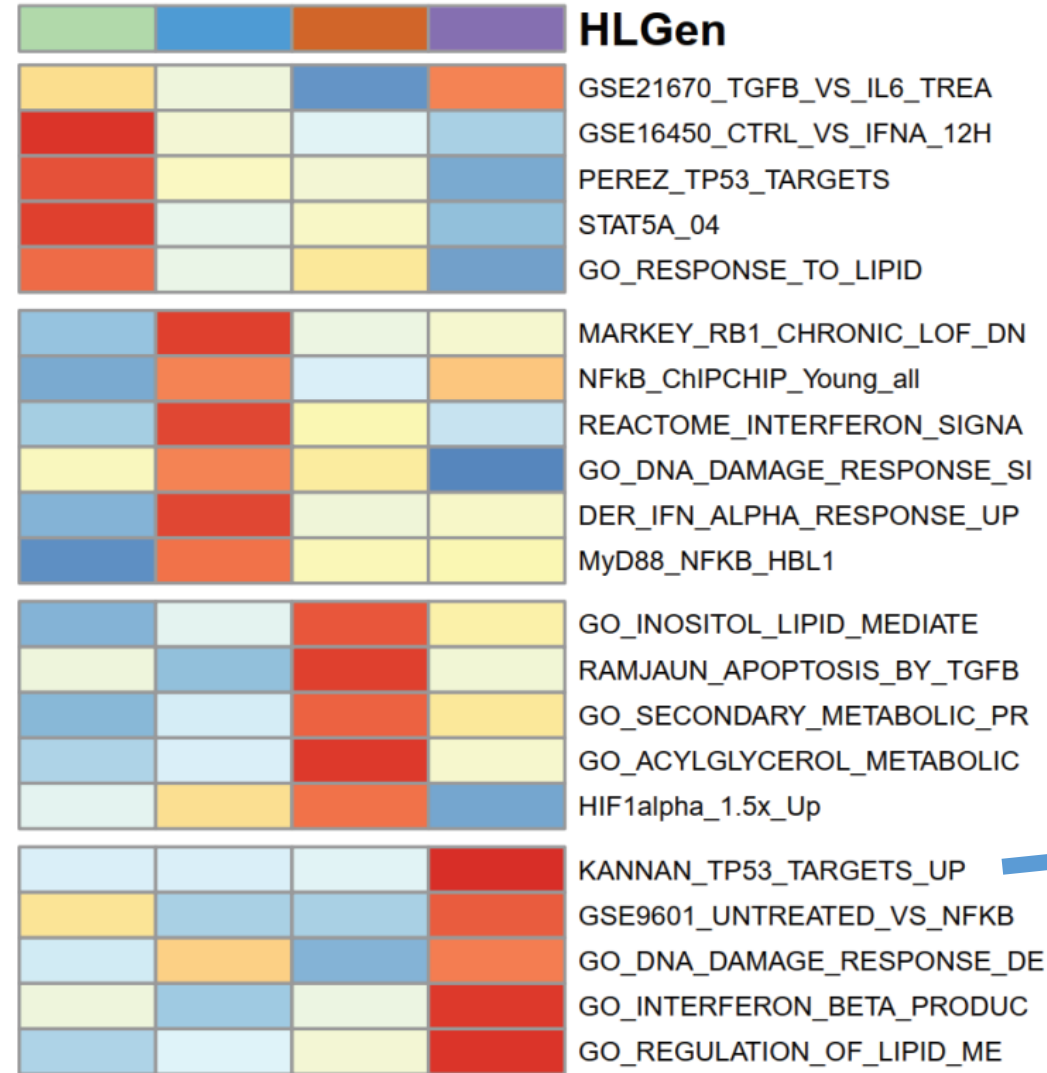


Discovery of four HL molecular subsets

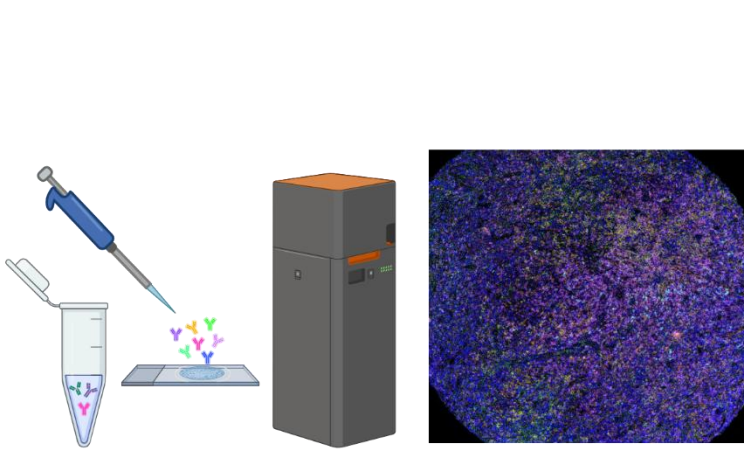


Distinct signaling/pathways of four CHL molecular subsets

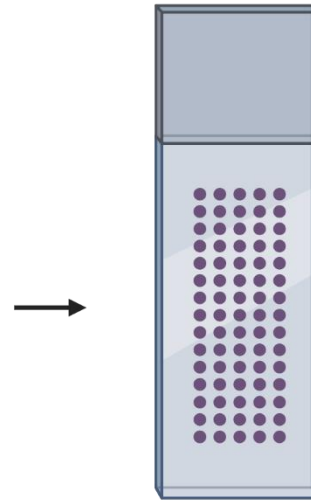
STAT5 NFkB TGFb DNA Damage



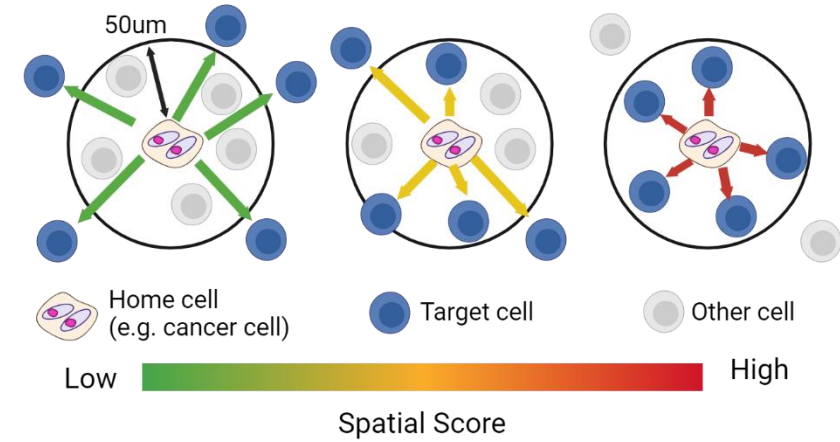
Imaging mass cytometry study overview



Imaging mass cytometry

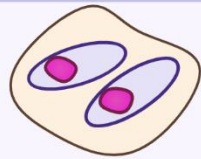


**Tissue Microarray
(N = 107)**



**Spatial characterization
(Spatial Score)**

HRS cells:
CD30, PD-L1, CCL17,
CD80, CD86, CXCR4



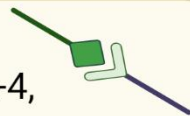
T cell:
CD3, CD4, CD8a, FOXP3, CCR4,
CXCL13, ICOS, Granzyme B, CXCR3



Myeloid:
CD68, CD163, CD11b, CD123,
CD11c, CD14, CD47, Galectin-9



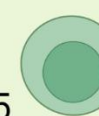
Immune check point:
PD-1, LAG-3, TIM-3, CTLA-4,
CLEC2D



Stroma; Cells:
aSMA, Vimentin,
CXCL12, Fibronectin



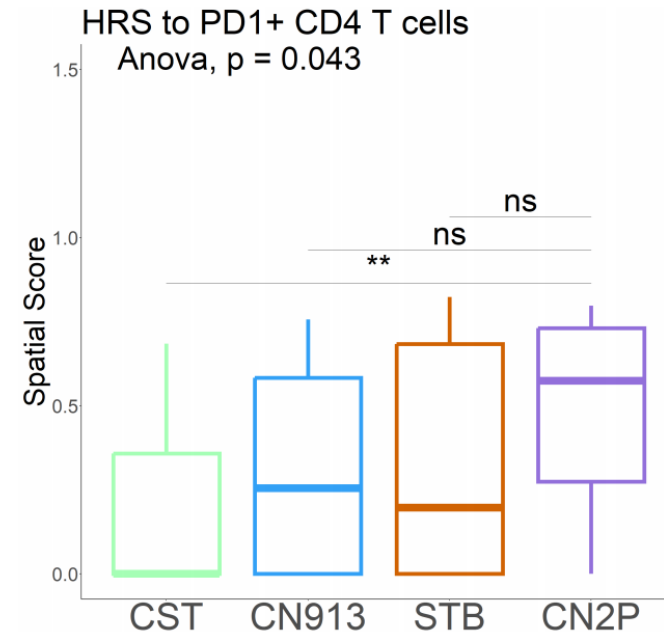
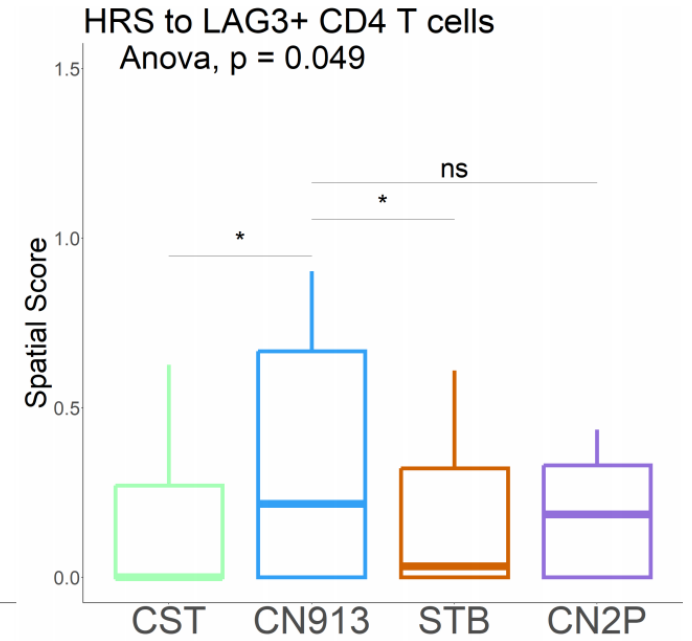
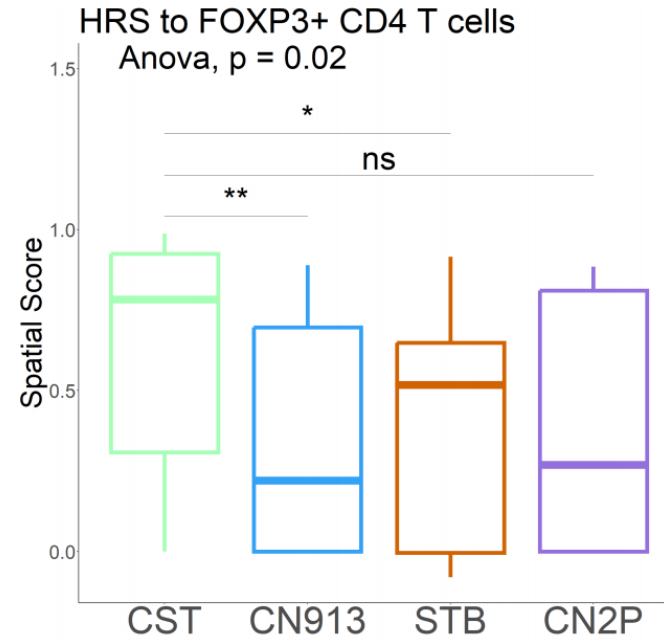
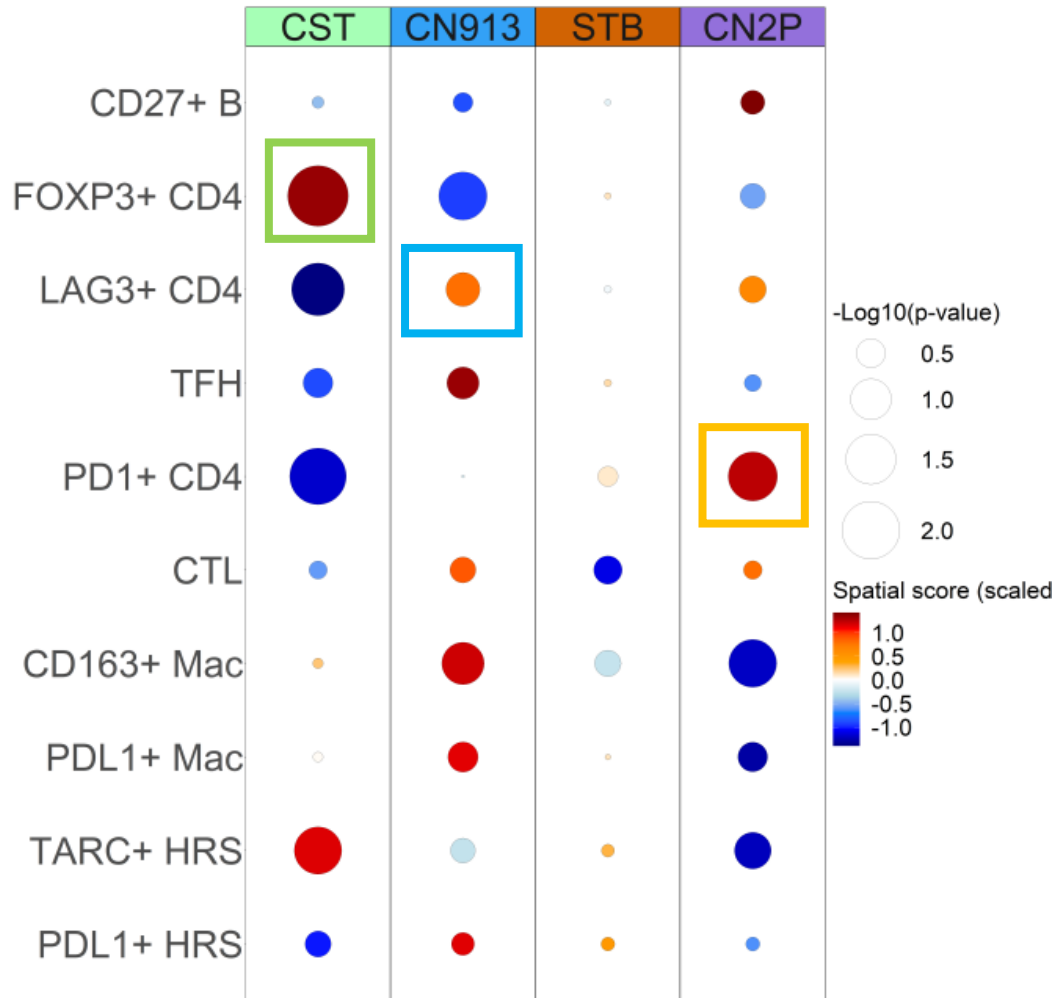
B Cell:
CD20, CD27,
BCL6, CXCR5



Others:
Ki67, TGF-B

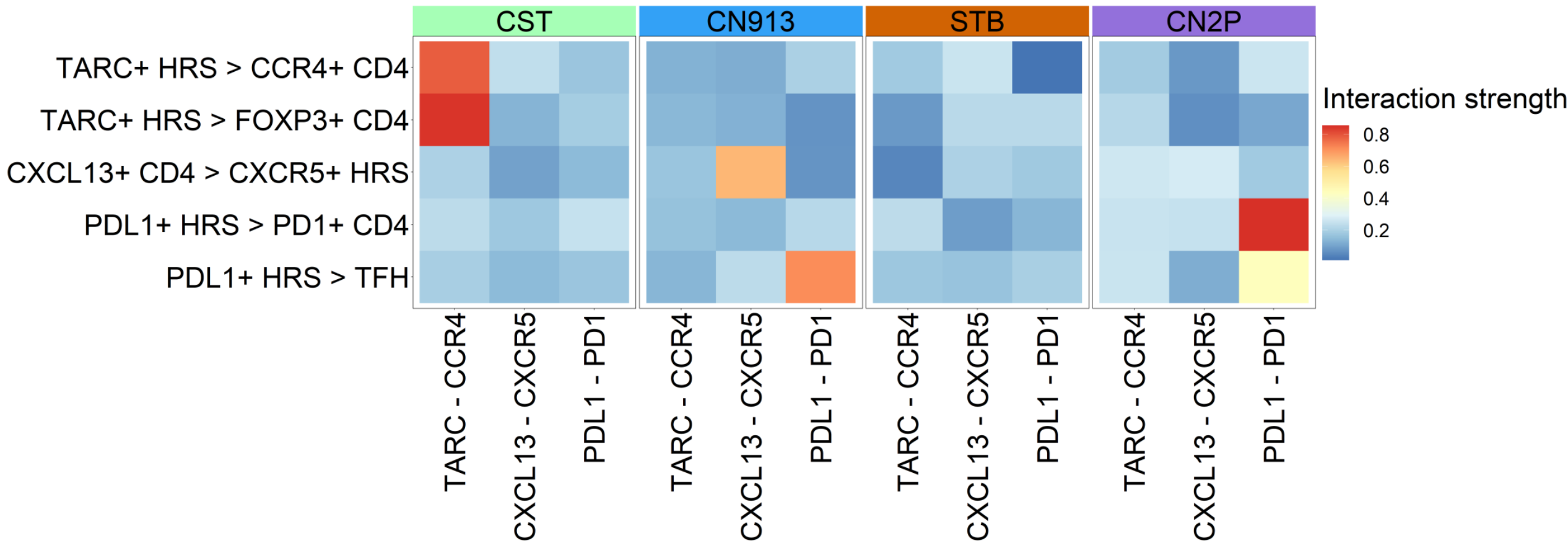


Each molecular cluster showed unique correlations with specific TME subset

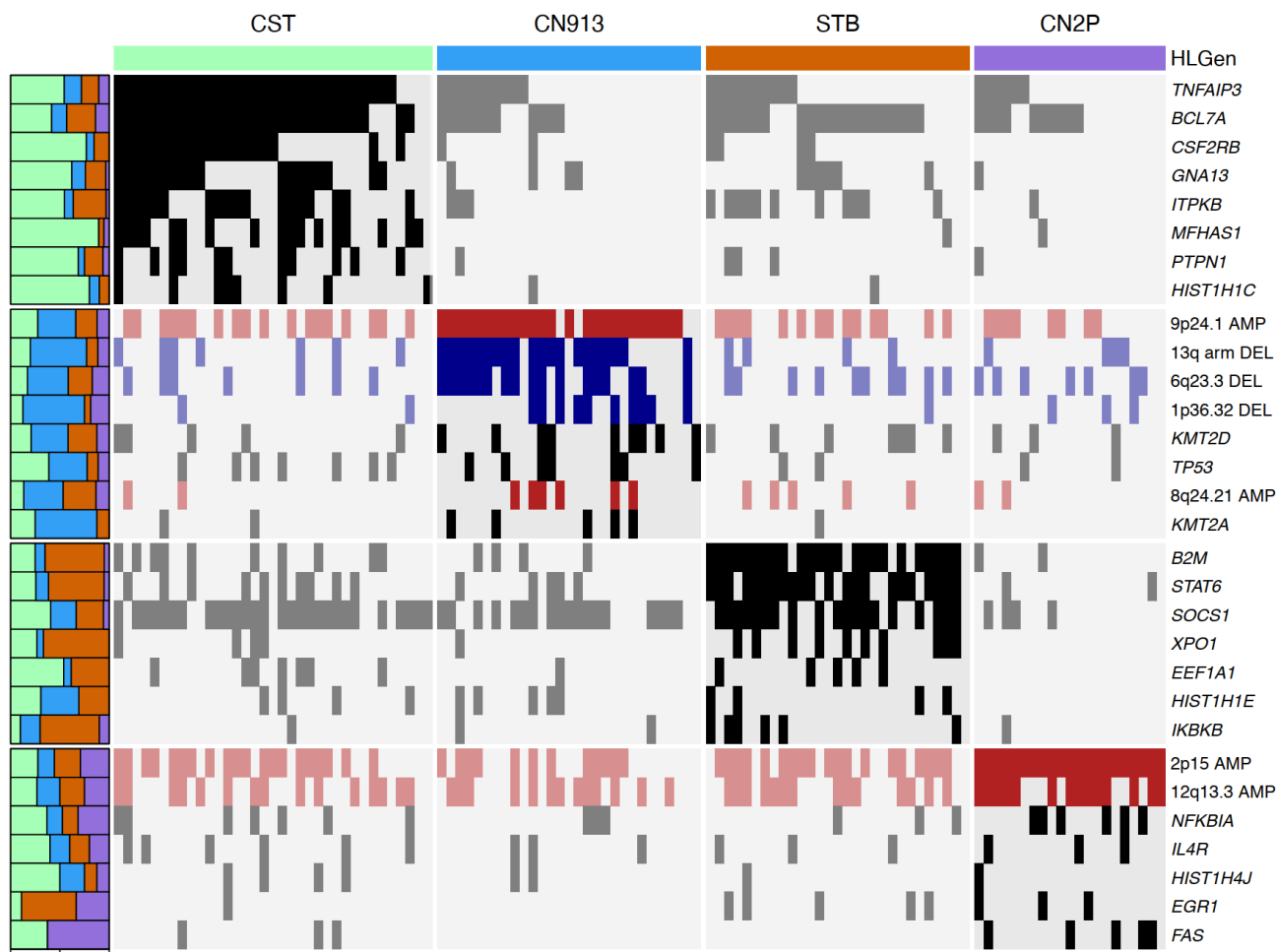


Each molecular subtype showed unique correlations with specific CD4 T cells

Each molecular cluster showed the distinct significant interactions



Molecular heterogeneity and their contribution to TME



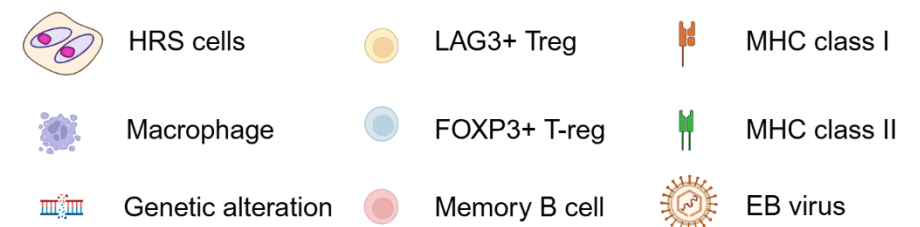
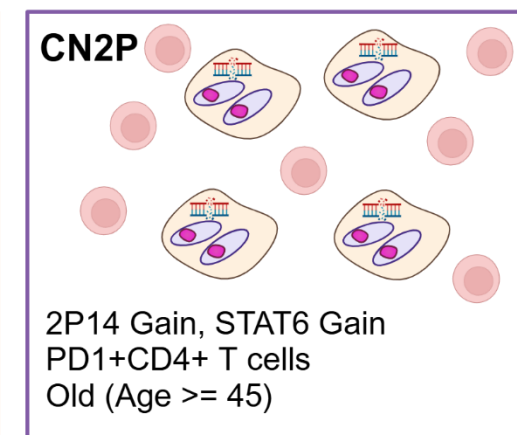
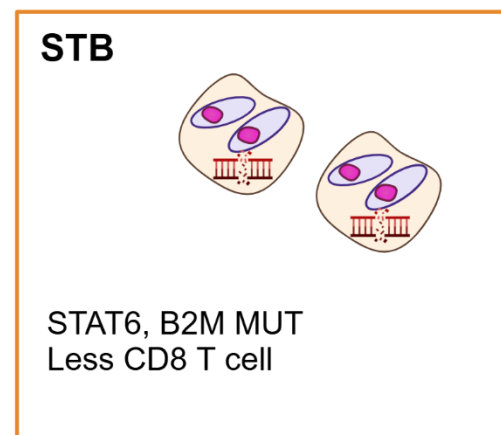
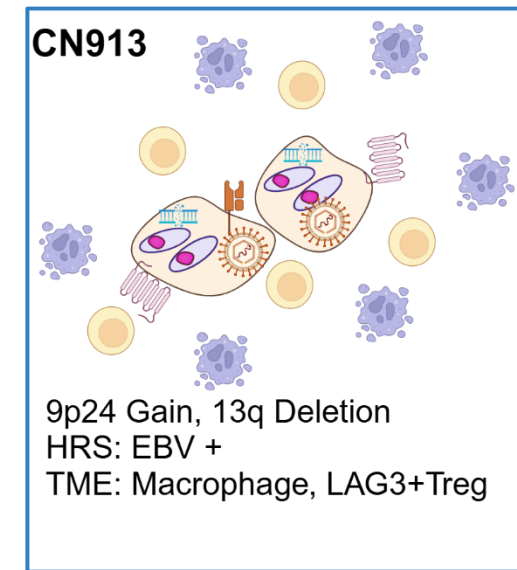
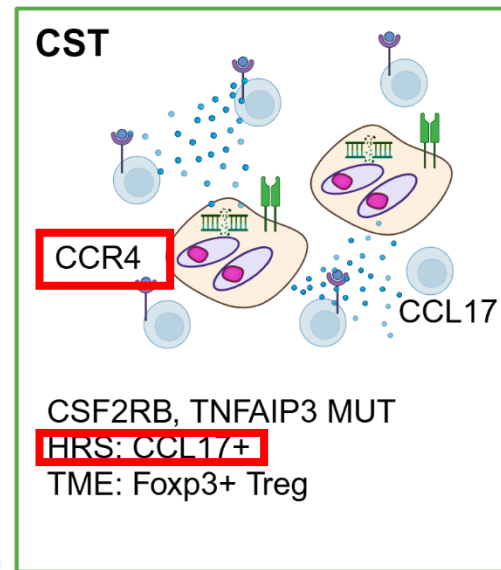
0 0.5 1
Proportion

CSF2RB
TNFAIP3

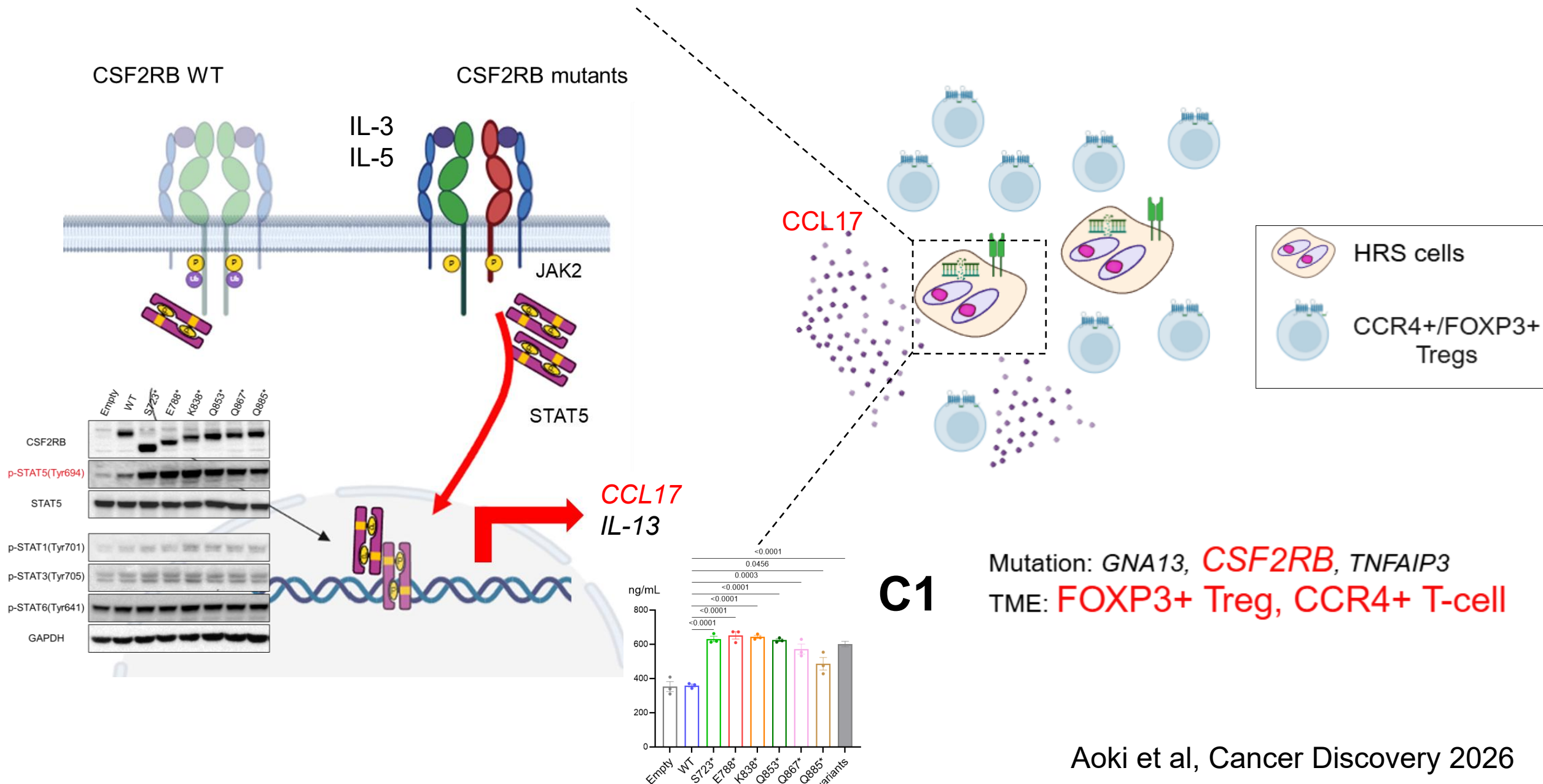
PDL1/2
Amp
13q DEL

STAT6
B2M
XPO1

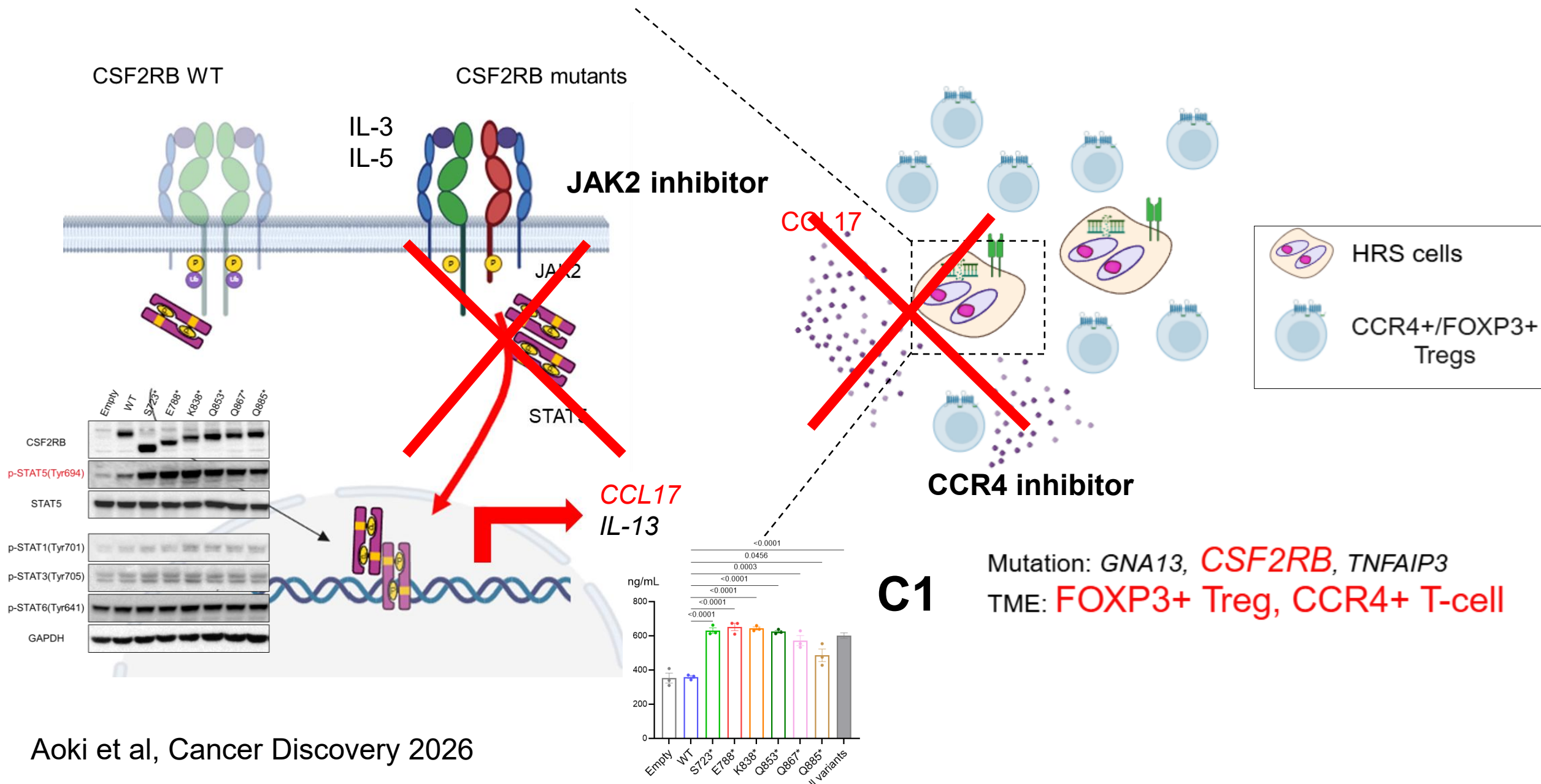
REL
STAT6
Gain



CSF2RB driven CCL17/CCR4 interaction in the TME of HL

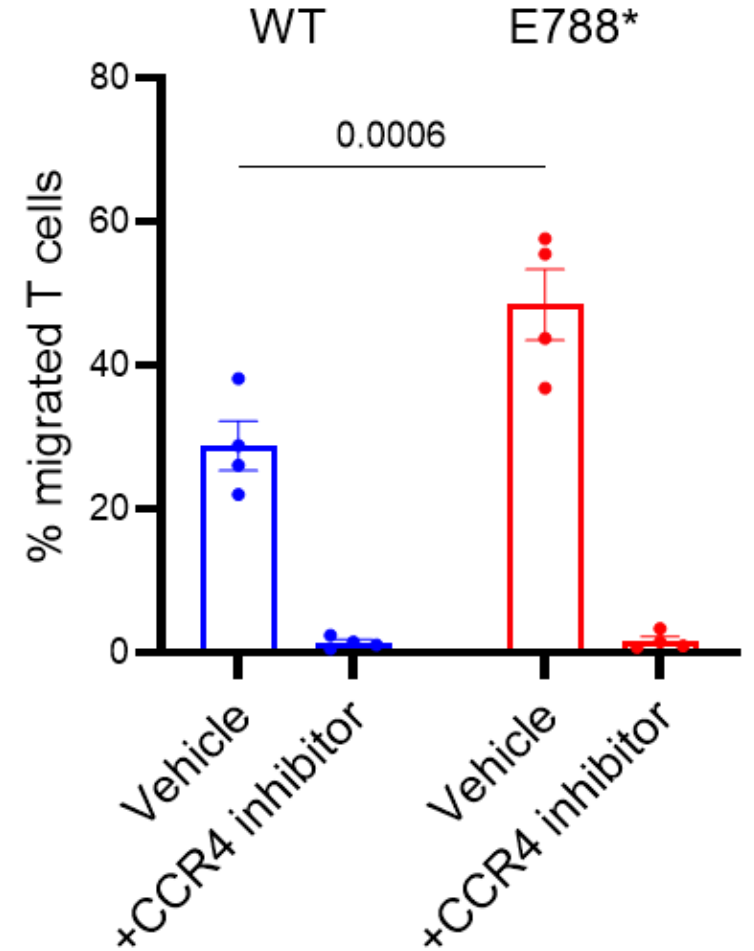
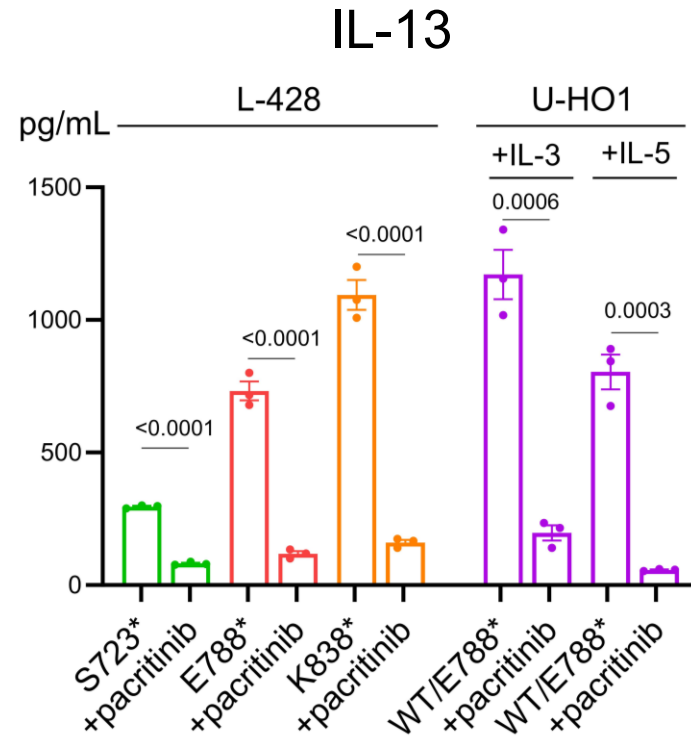
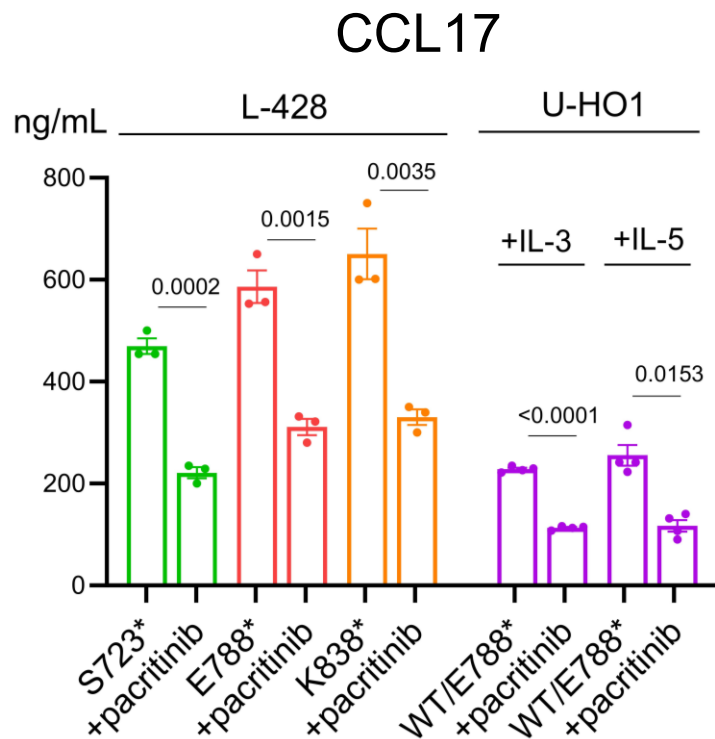


The gain-of-function effects were inhibited by JAK2/CCR4 inhibitor



The gain-of-function effects were inhibited by JAK2/CCR4 inhibitor

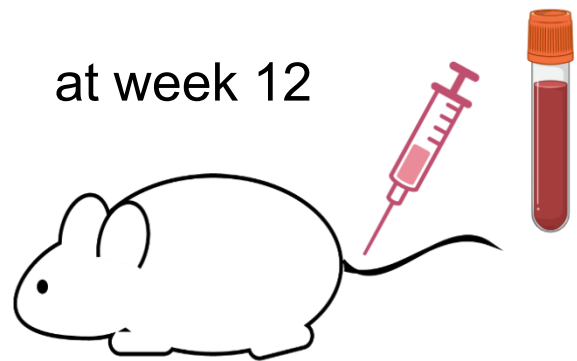
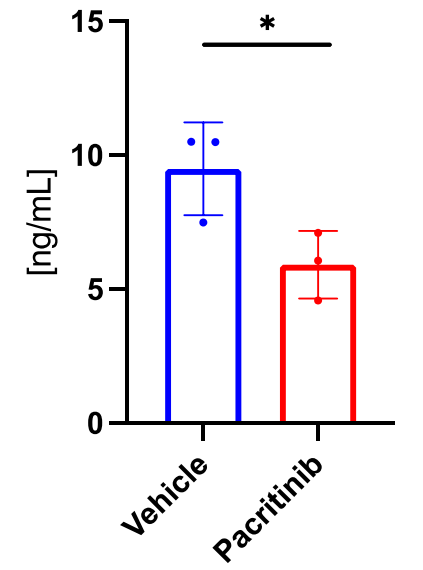
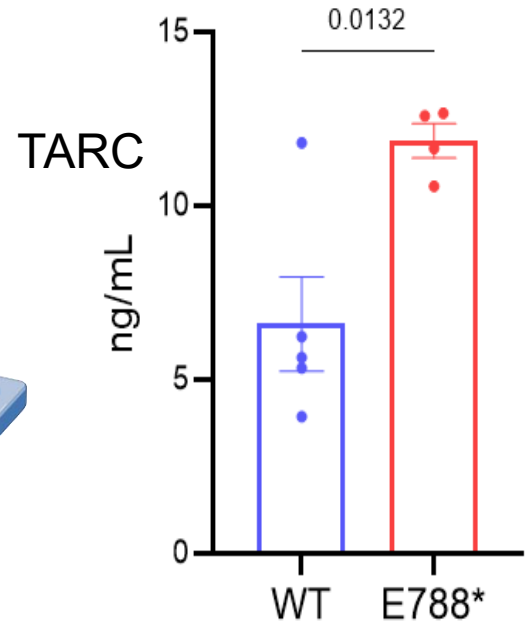
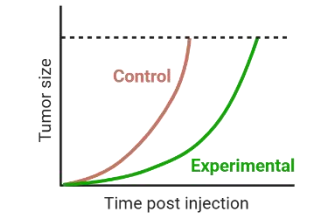
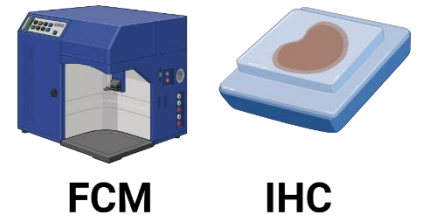
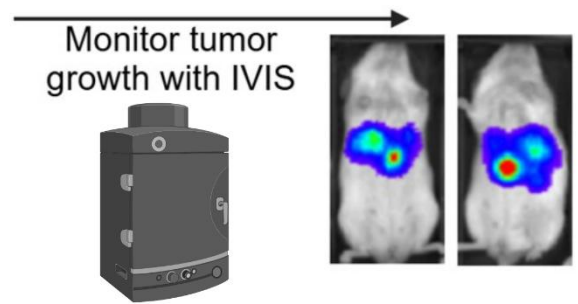
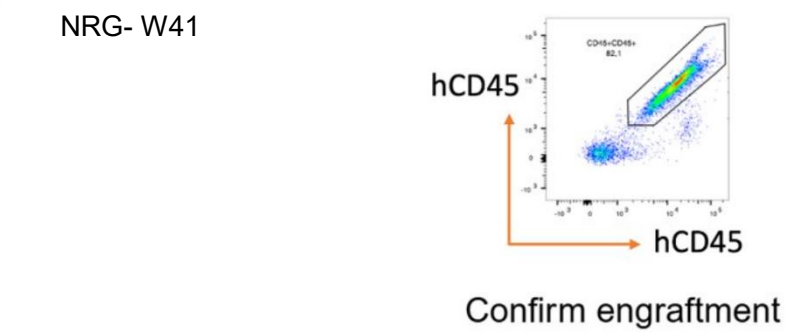
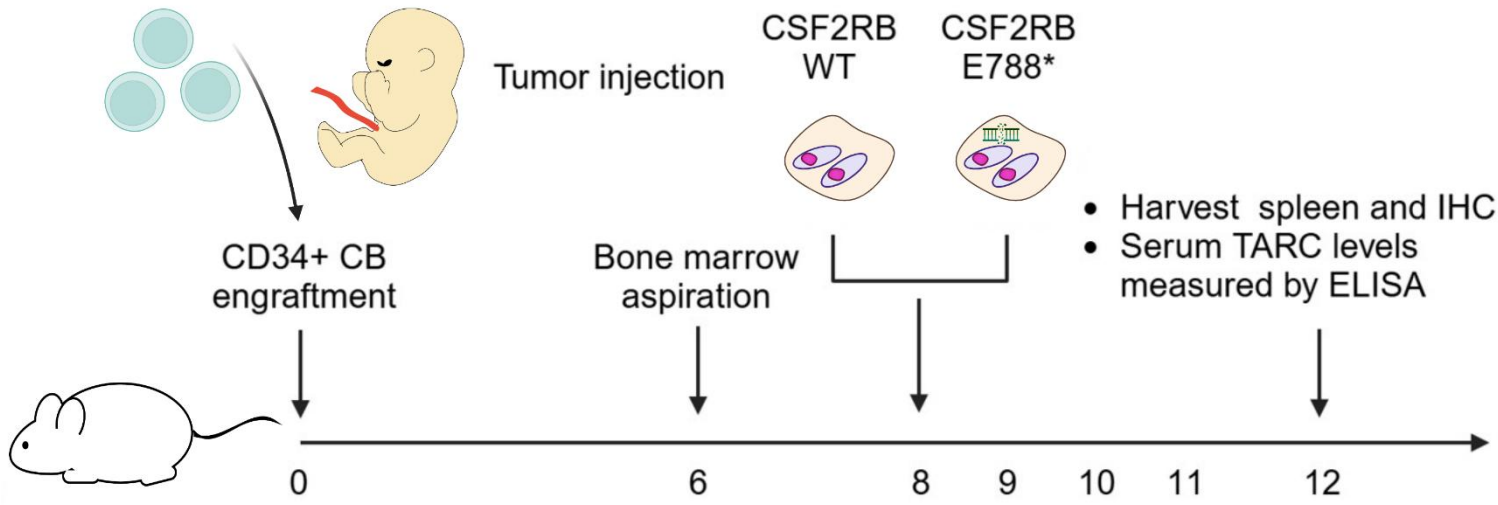
These gain of functions were JAK2 dependent



Pacritinib: a selective JAK2 inhibitor

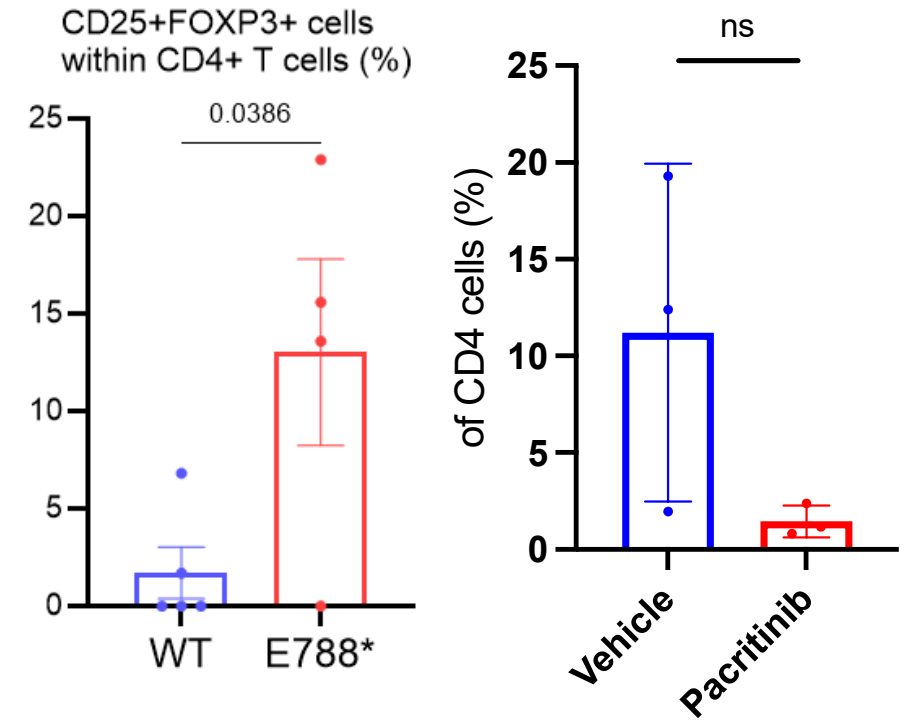
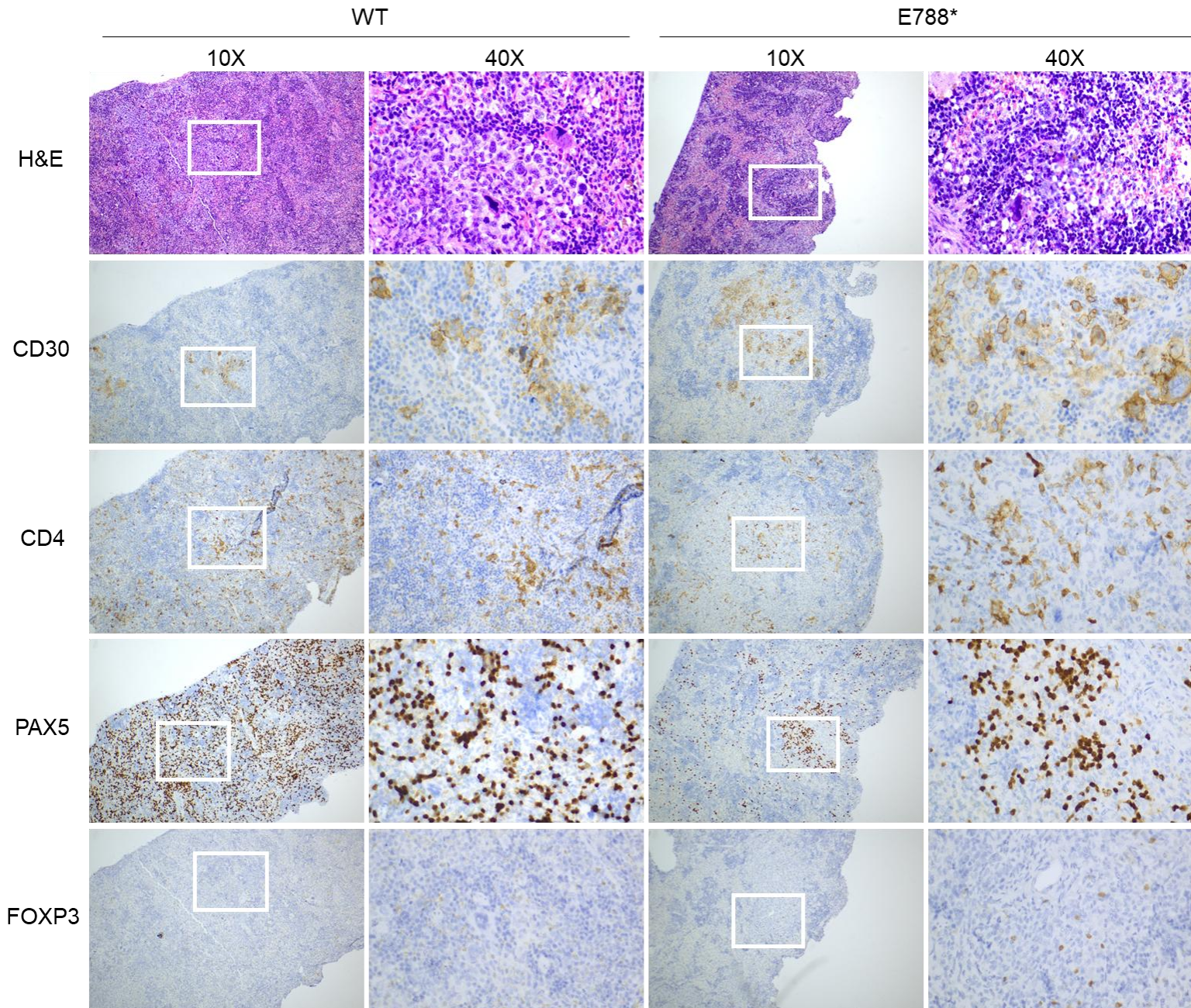
Migration phenotype: CCR4 dependent

CSF2RB-carrying humanized mouse xenotransplantation model



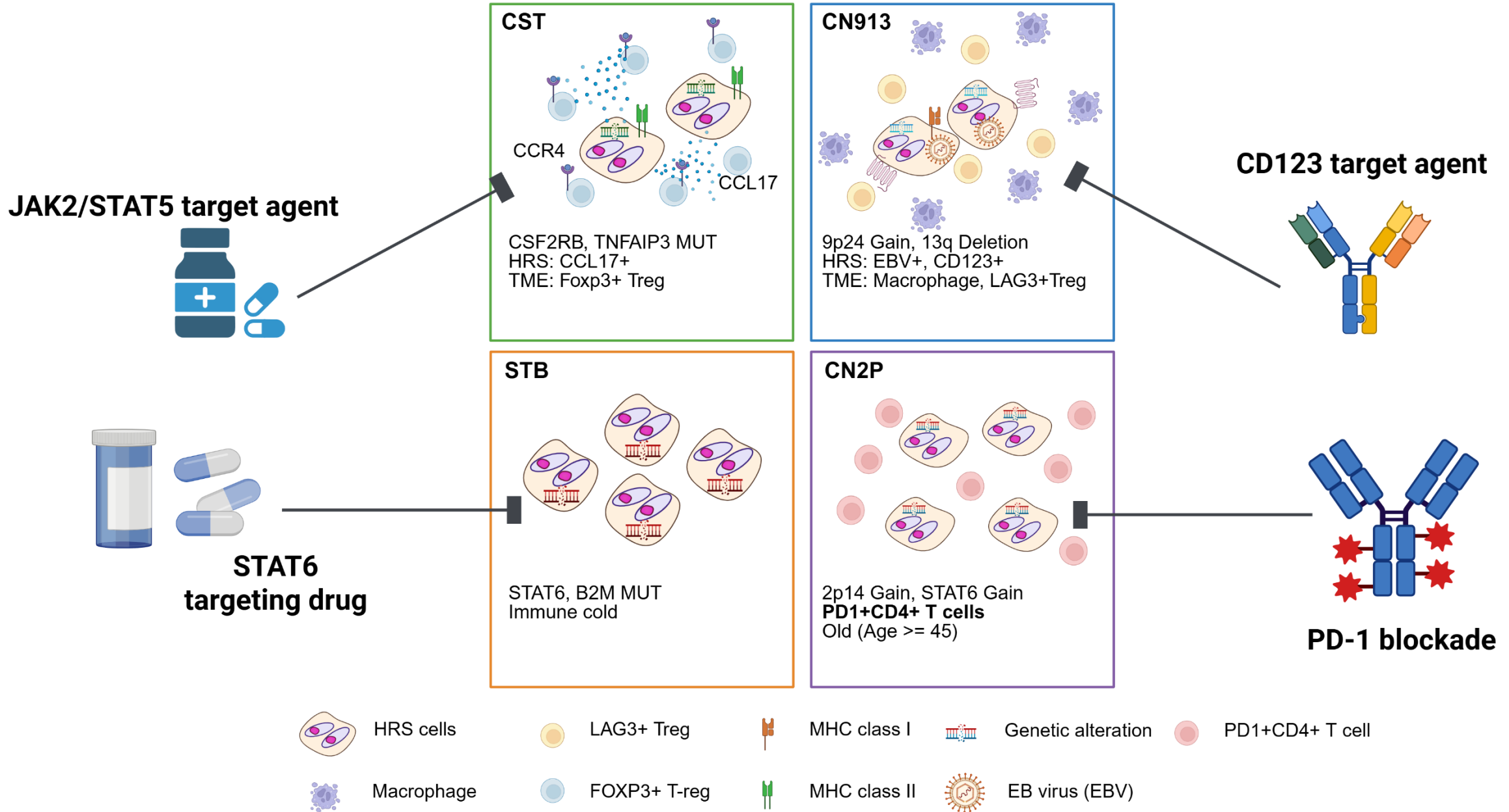
Serum TARC(CCL17) level

CSF2RB-carrying humanized mouse xenotransplantation model

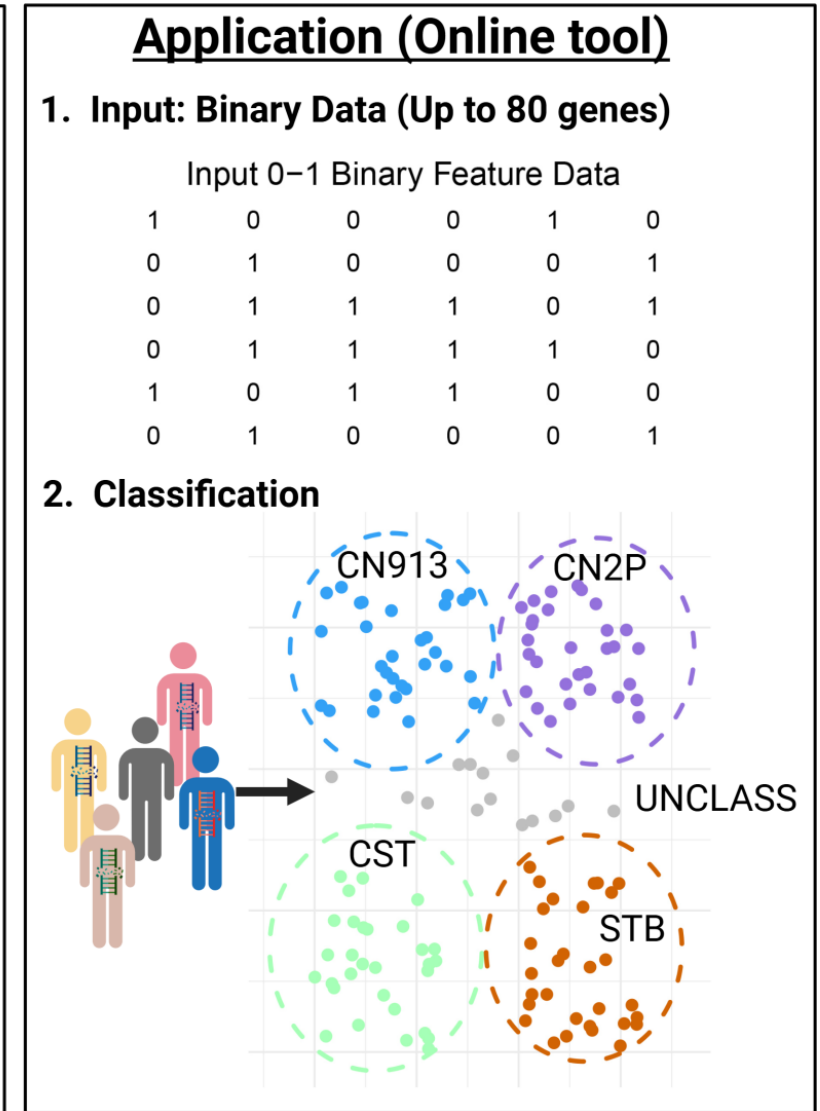
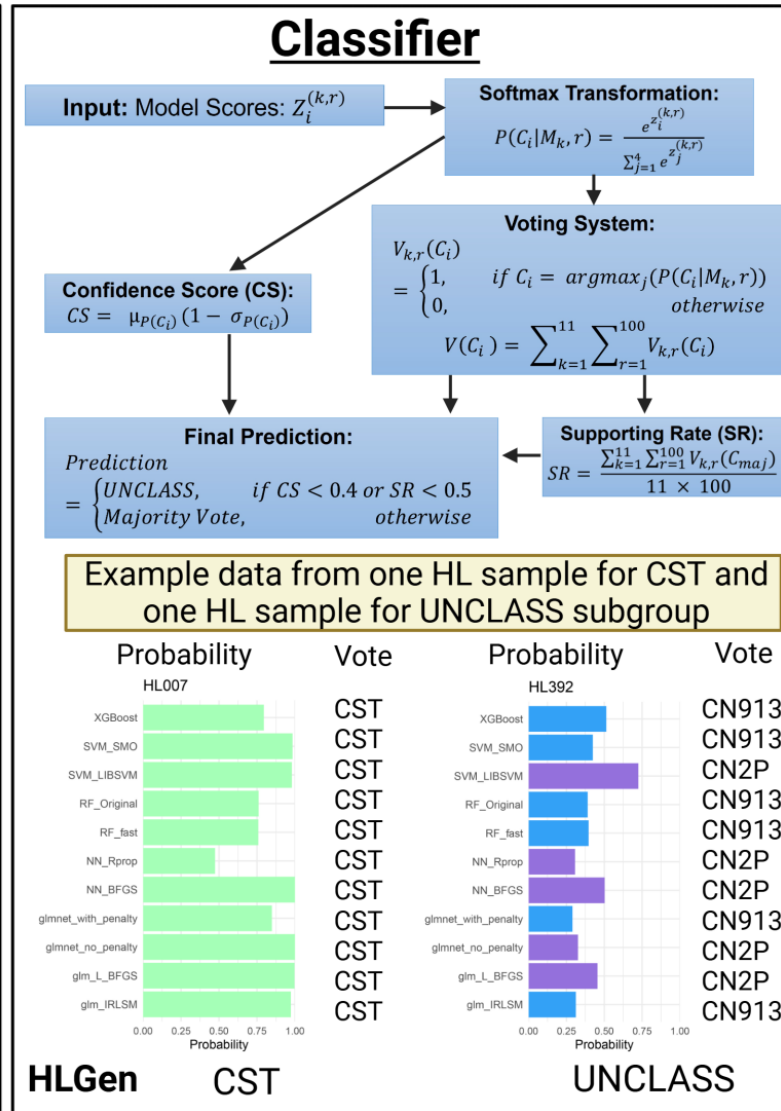
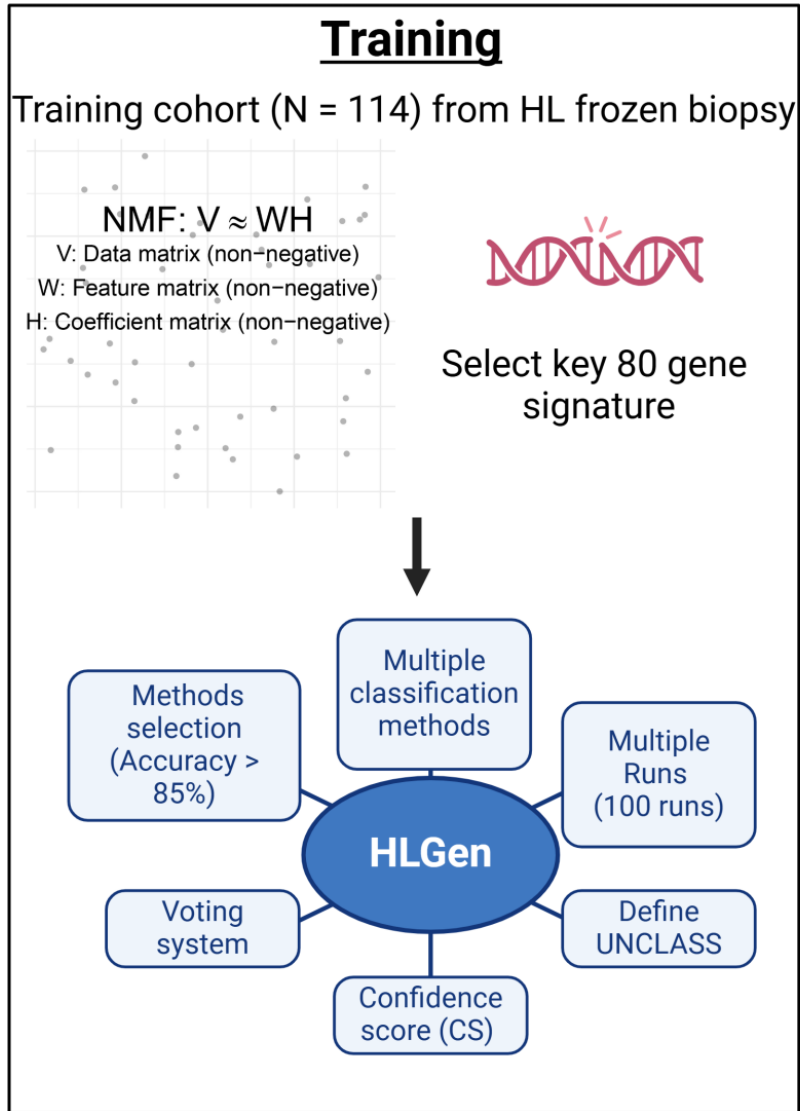


Reproduce FOXP3 enriched TME
In mice

Next STEP: Establish biology driven treatment strategy according to molecular subgroup

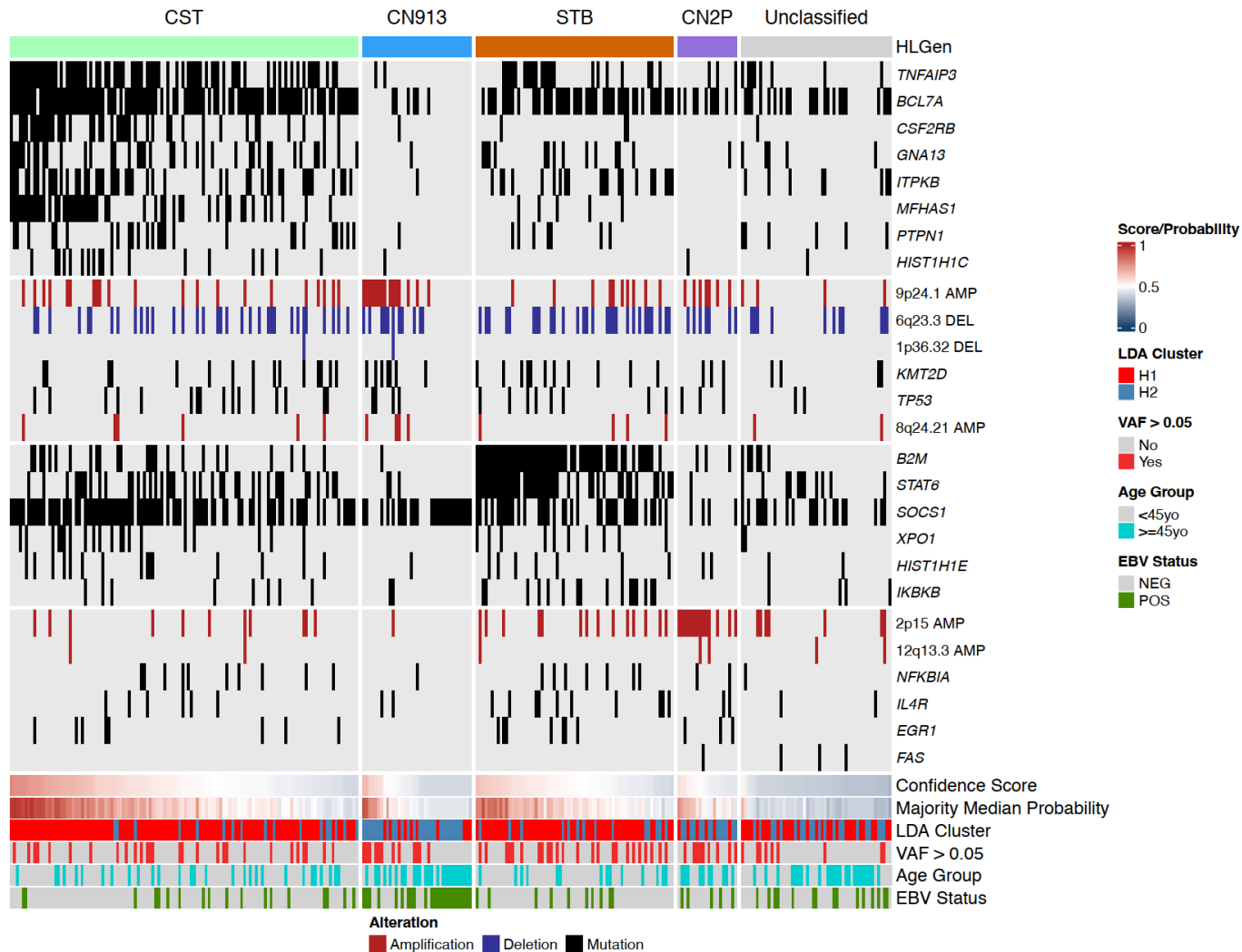


Establishment of molecular classification system: HLGen

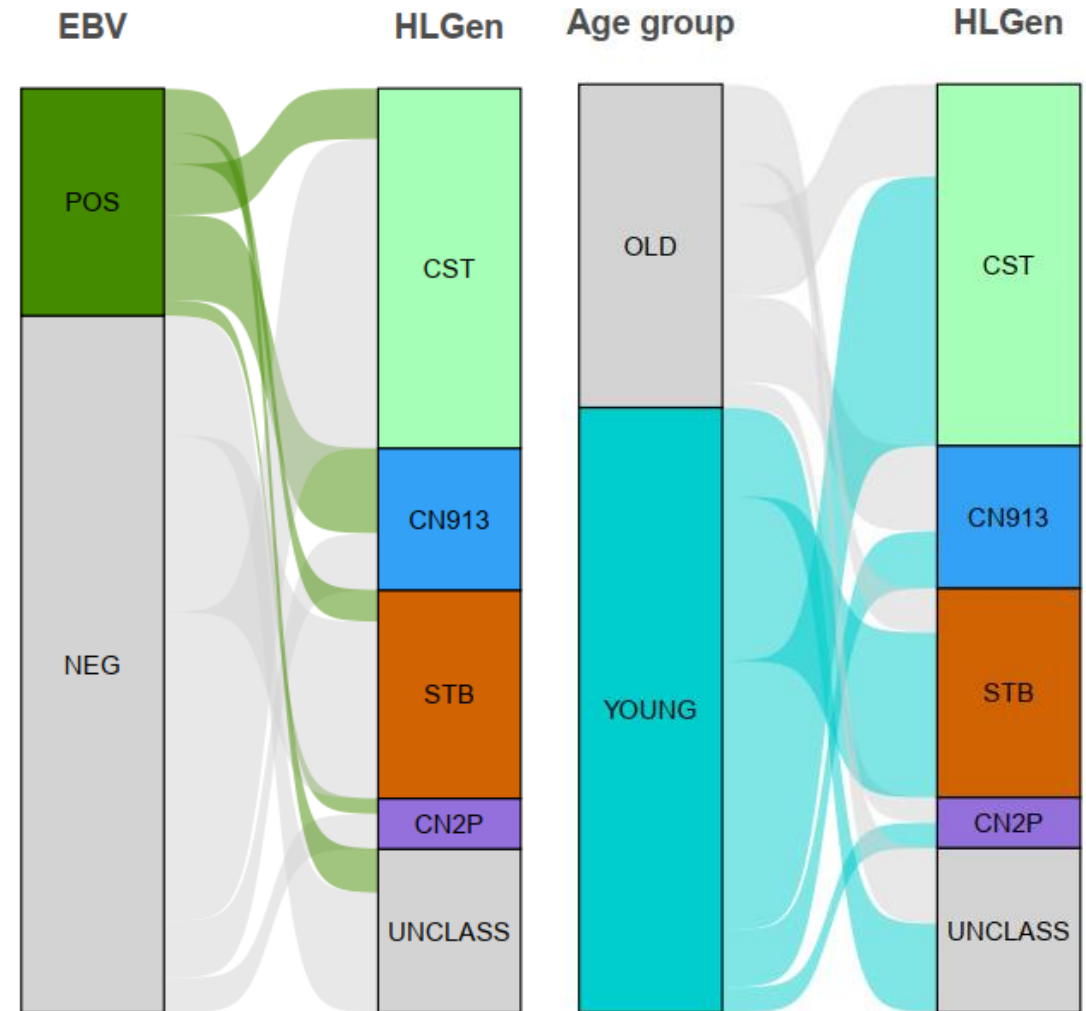


HLGen: Real-time application and individual patient at <https://shiny.bcgsc.ca/HLGen/>

Validation of four HL molecular subsets: ctDNA Stanford cohort

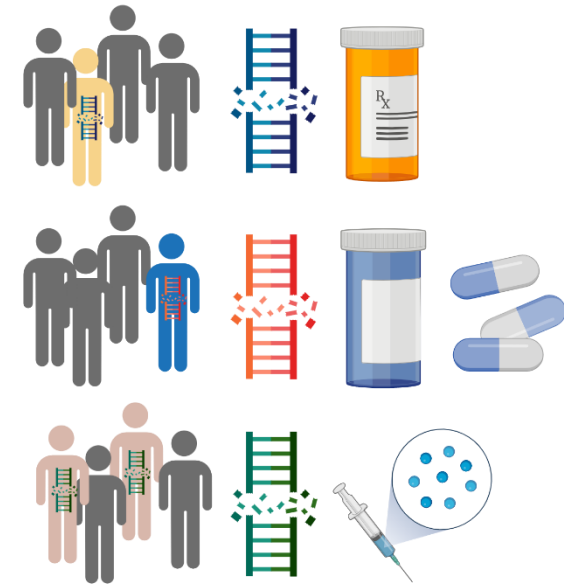
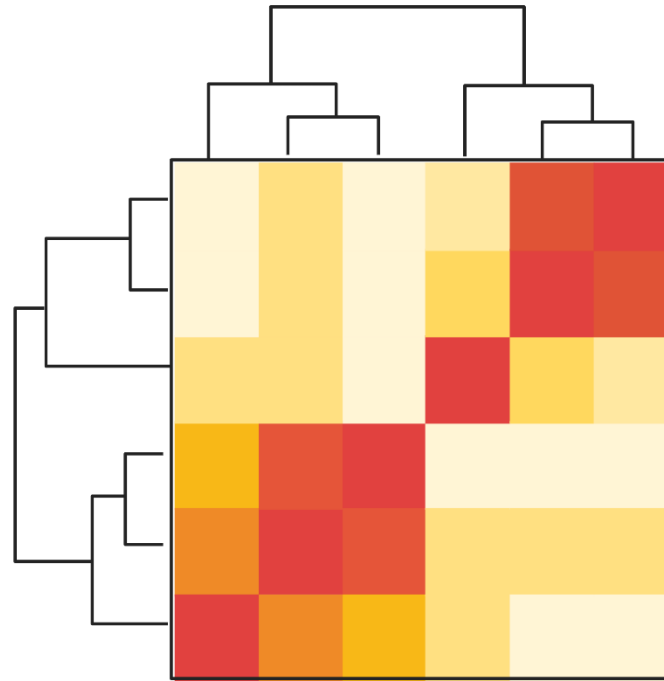


CSF2RB 9p GAIN ***STAT6*** 2p GAIN
TNFAIP3 13q DEL ***B2M*** 12q GAIN
MFHAS1 ***XPO1***



Summary and conclusions

- HL: Heterogeneous molecular profiles
 - Mutational Burden
 - Age
 - EBV
 - Signaling pathway
 - TME



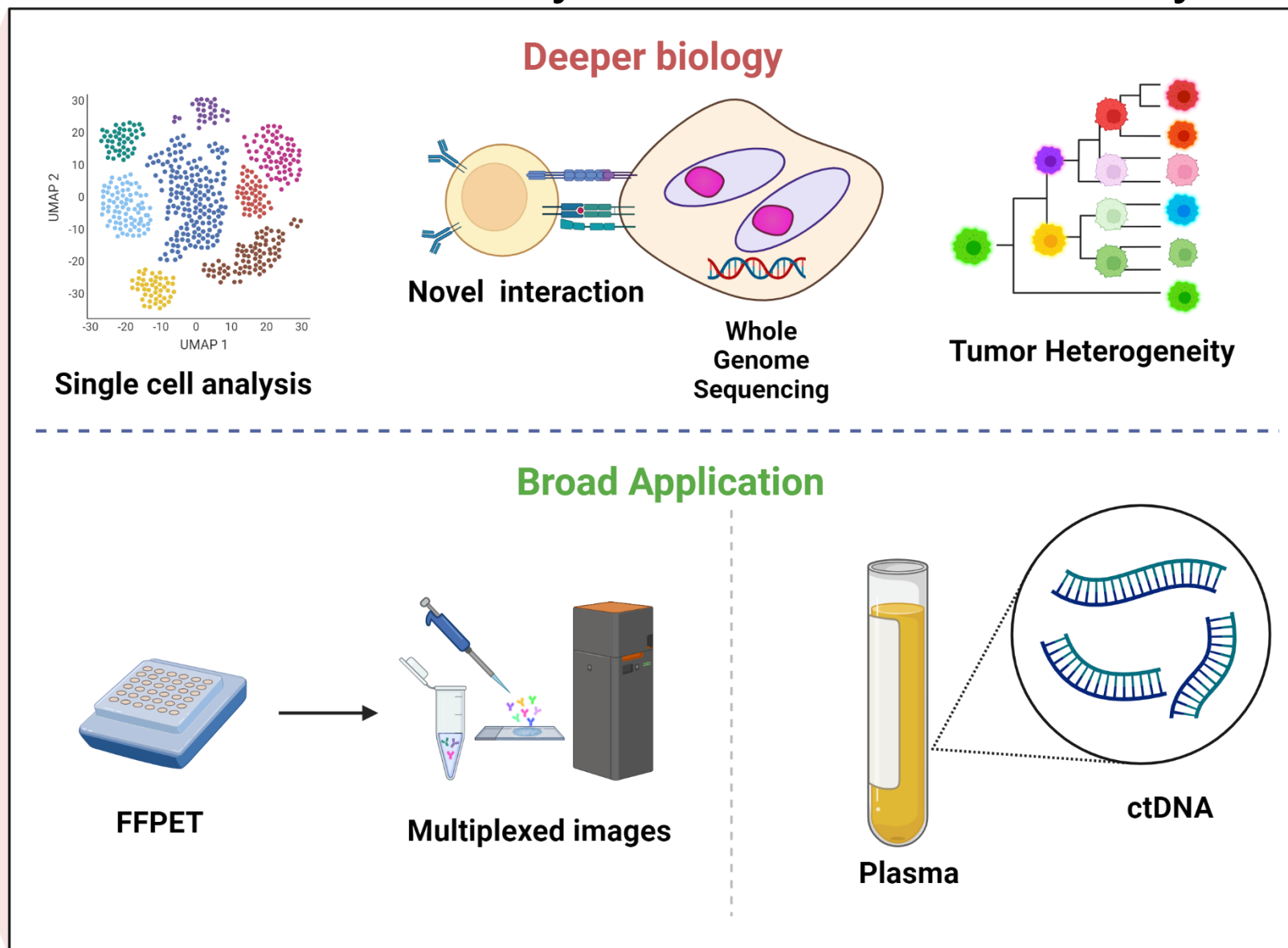
Precision Medicine

Next STEP

- Clinical application
- Guide Treatment

FFPE and liquid biopsy-based assay has expanded applicability of spatial/molecular assay in routine clinical analyses

Any lymphoma



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Katsuyoshi Takata

Patients + Families



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 Sharon Castelino
 Kara Kelly

Sick Kids

Angela Punnett
 Nawar Dakhallah
 Bo Ngan
 Rose Chami

March 28th, 2026



Thank you!

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