TCR repertoire divergence reflects the microenvironmental immune phenotype in glioma

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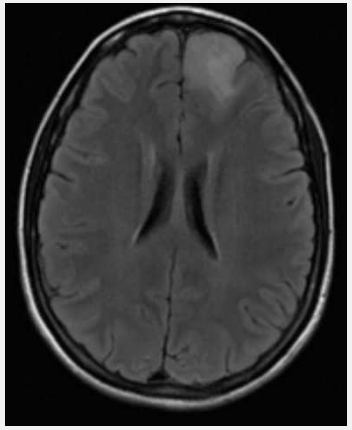
PRESENTER DISCLOSURE INFORMATION

Jennifer Sims: No Relationships to Disclose!

All other authors: No Relationships to Disclose!

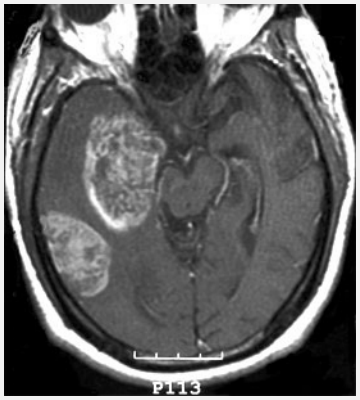


Low-grade glioma

- Long prognosis (>10yr)
- Progresses to GBM

GBM

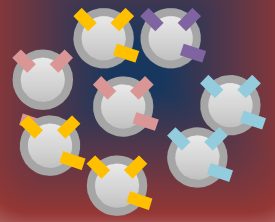
- Short prognosis
- Cx, Rx refractory
- Diffusely infiltrating
- Heterogeneous



ANTI-TUMOR REACTIVITY

IMMUNOSUPPRESSION

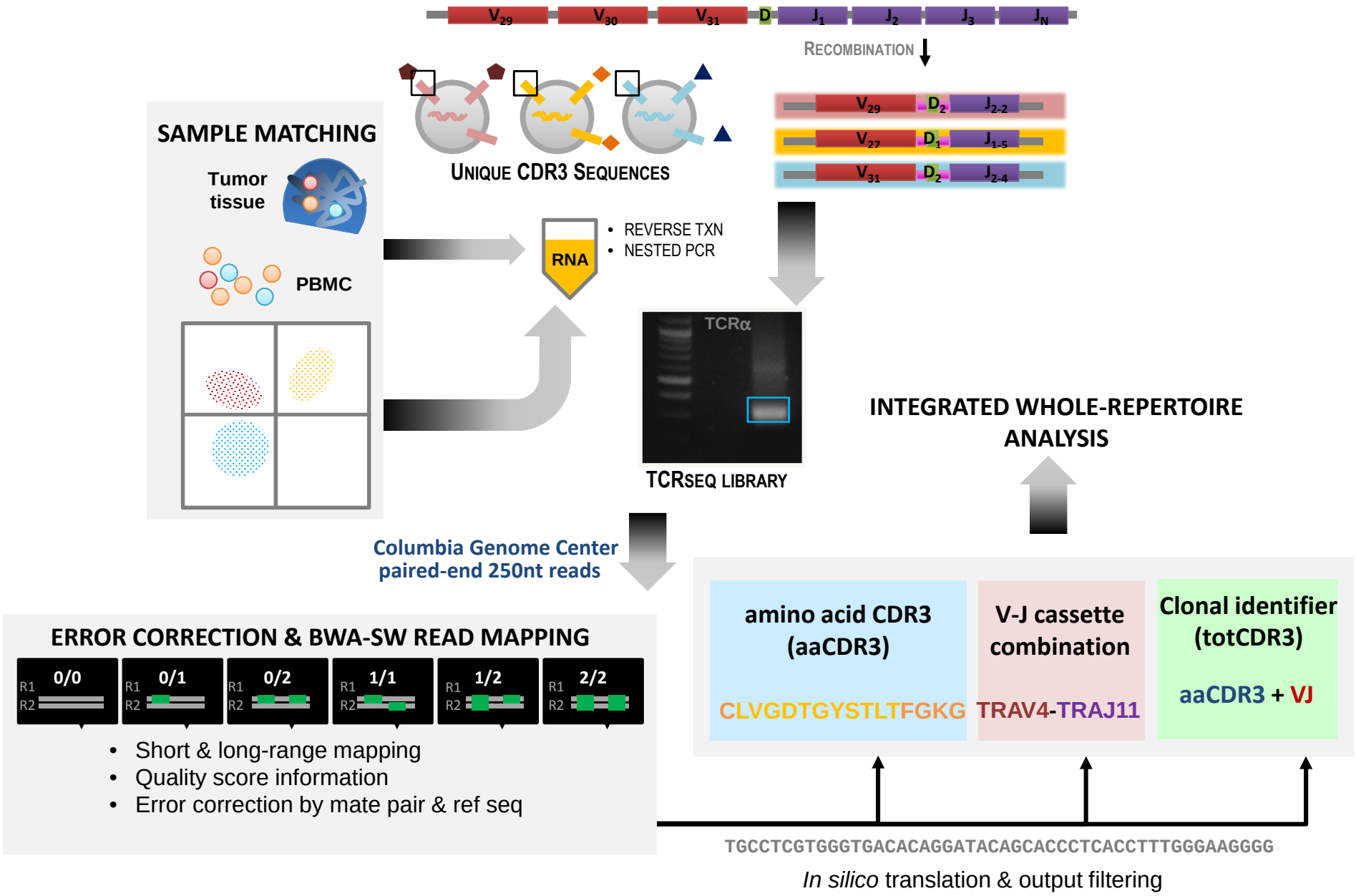
Peripheral T cells



- MDSC, T_{reg}
- Suppressive cytokines
- Tissue damage, necrosis, hypoxia

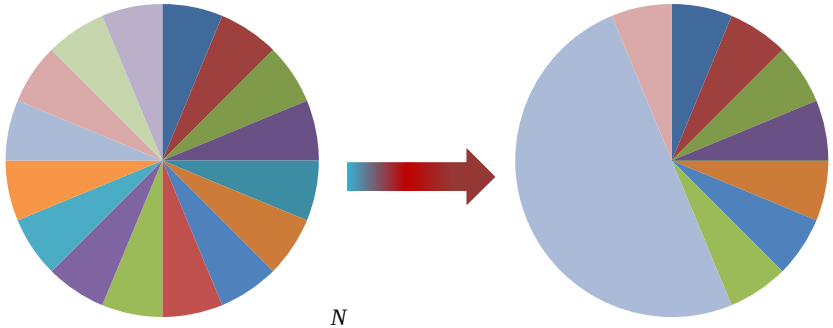
- Leukopenia
- NKT, T_{reg}, CD8/CD4
- Exhaustion markers

ACCESSING T CELL REPERTOIRES BY TCRseq



MEASURING DIVERSITY & DIVERGENCE

SHANNON ENTROPY (H)



H = 4.00 $\sum_{i=0}^{N} - p_i \log_2 p_i$ H = 2.50

TGT.GTG.GTG.AAC.ATG.CCT.CTG.TGG.AGC.TAT.GGA.AAG.TTT.GGA.CAA.GGG

amino acid CDR3 (aaCDR3) CVVNMPLWSYGKFGQG

V-J cassette combination TRAV12-1.TRAJ52

Clonal identifier (totCDR3) aaCDR3 + VJ

TRAV12-1.TRAJ52 CVVSMPPLWAGGTSYGKLTFGQG

CVVNMPPLWACGTSYGKLTFGQG

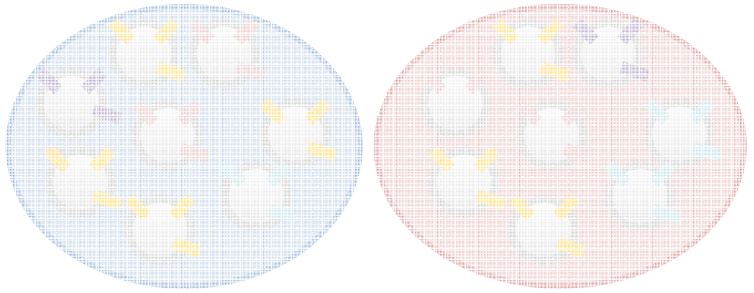
CVVNPLAGGTSYGKLTFGQG

CLONALITY

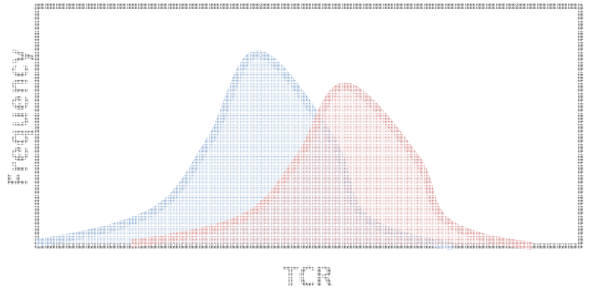
$$1 - \frac{H}{H_{max}}$$

$$CL = 1 - \frac{2.50}{4.00} = 0.375$$

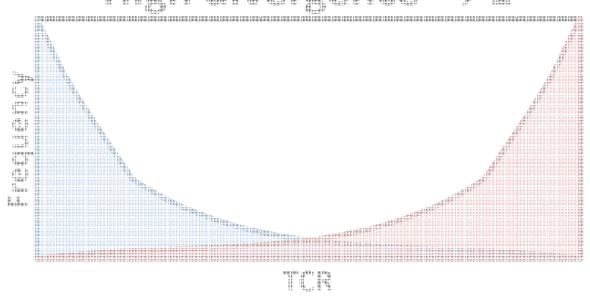
JENSEN-SHANNON DIVERGENCE METRIC (JSM)



Low divergence → 0



High divergence → 1

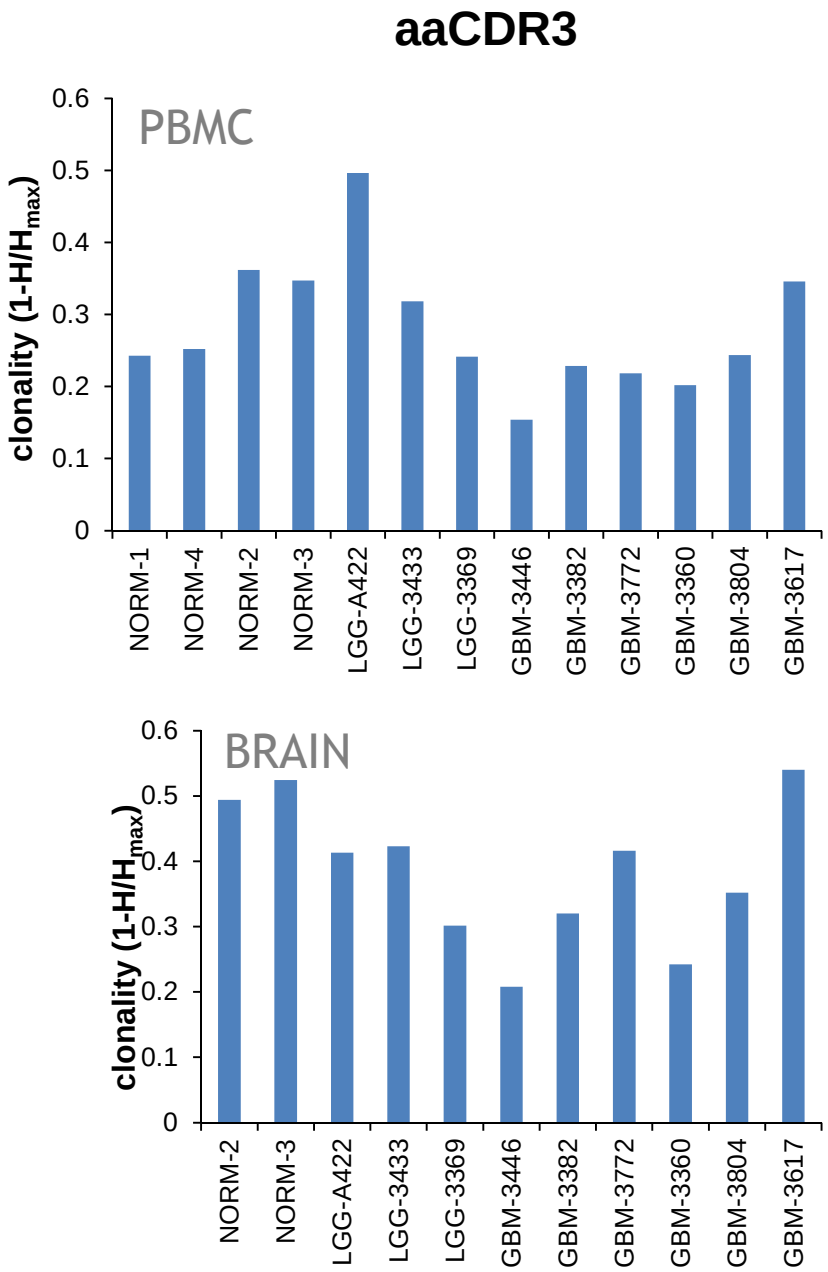


What features of the tumor microenvironment predict the state of the TCR repertoire?

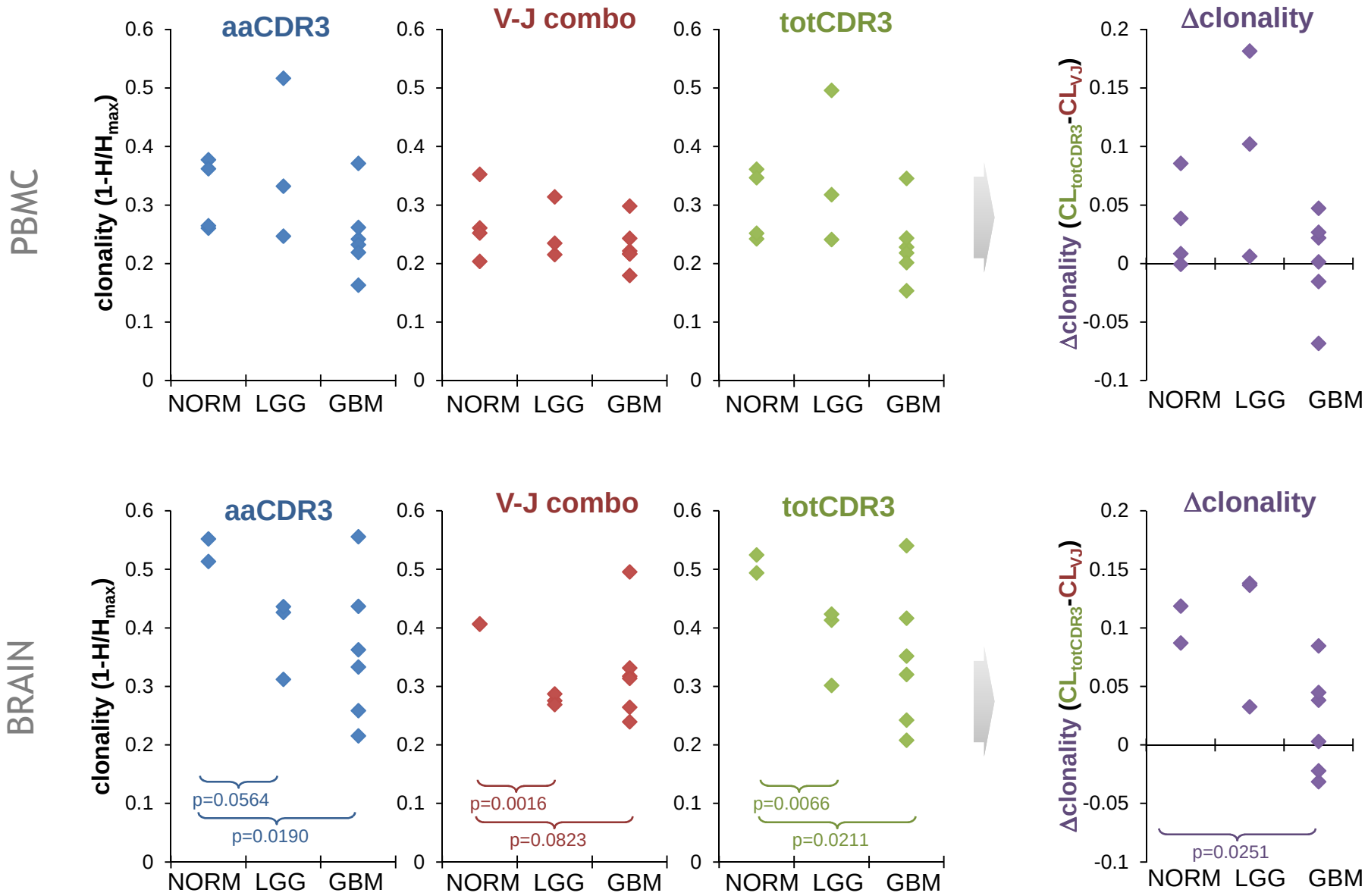
Can we use the TCR repertoire as a functional assay for perturbations to the tumor microenvironment?

CLONALITY OF TIL & PBMC TCR REPERTOIRES

DIAGNOSIS	AGE	M/F
Astrocytoma, Grade II	33	F
Oligodendroglioma, Grade II	59	F
Oligodendroglioma, Grade II	25	M
GBM, Grade IV	53	M
GBM, Grade IV	57	M
GBM, Grade IV	60	F
GBM, Grade IV	55	M
GBM, Grade IV	68	M
GBM, Grade IV	36	F
Normal cortex	79	M
Normal cortex	45	M

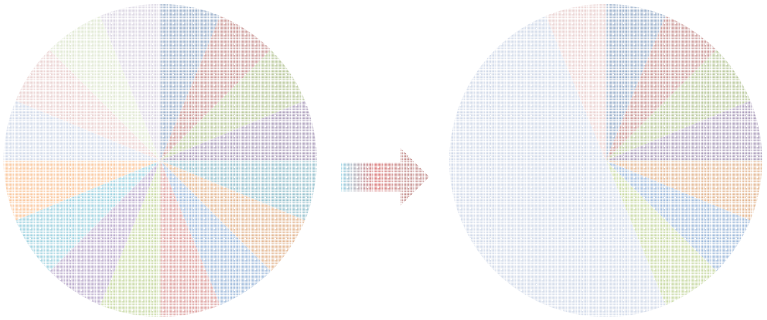


CLONALITY OF TIL & PBMC TCR REPERTOIRES

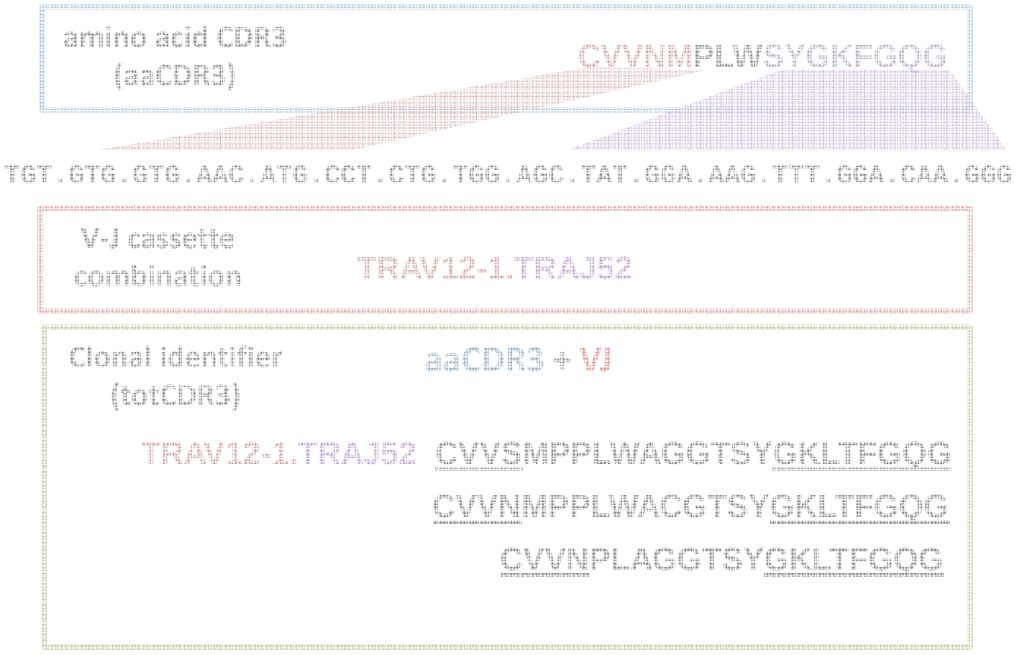


MEASURING DIVERSITY & DIVERGENCE

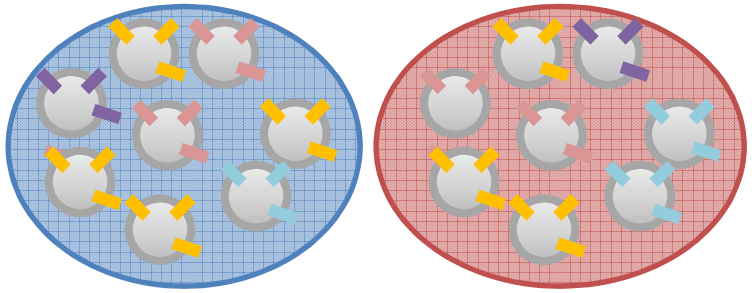
SHANNON ENTROPY (H)



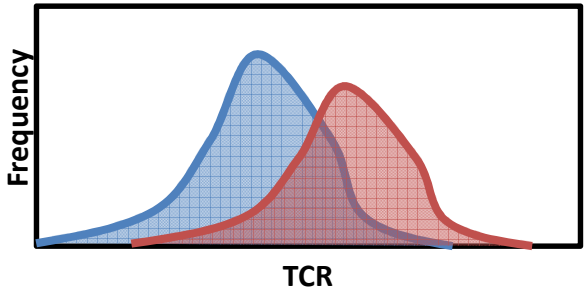
$$\sum_{i=0}^{N} -p_i \log_2 p_i$$



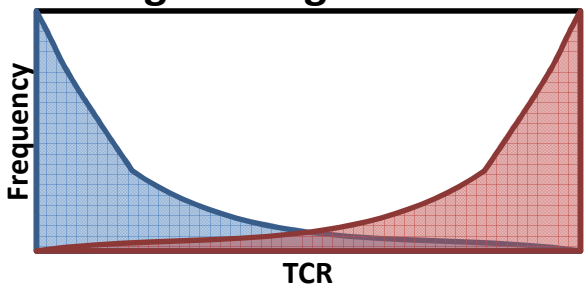
JENSEN-SHANNON DIVERGENCE METRIC (JSM)



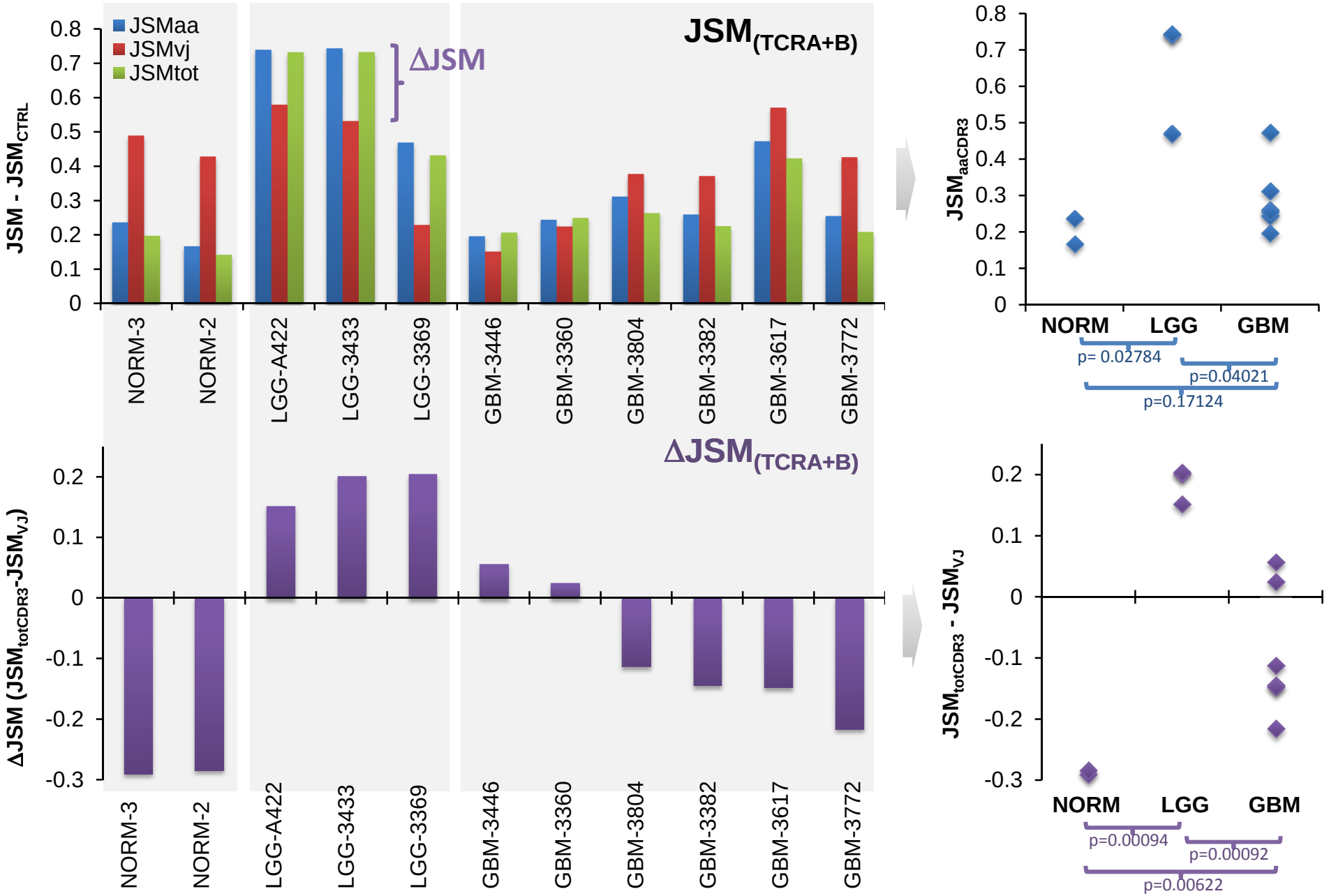
Low divergence → 0



High divergence → 1

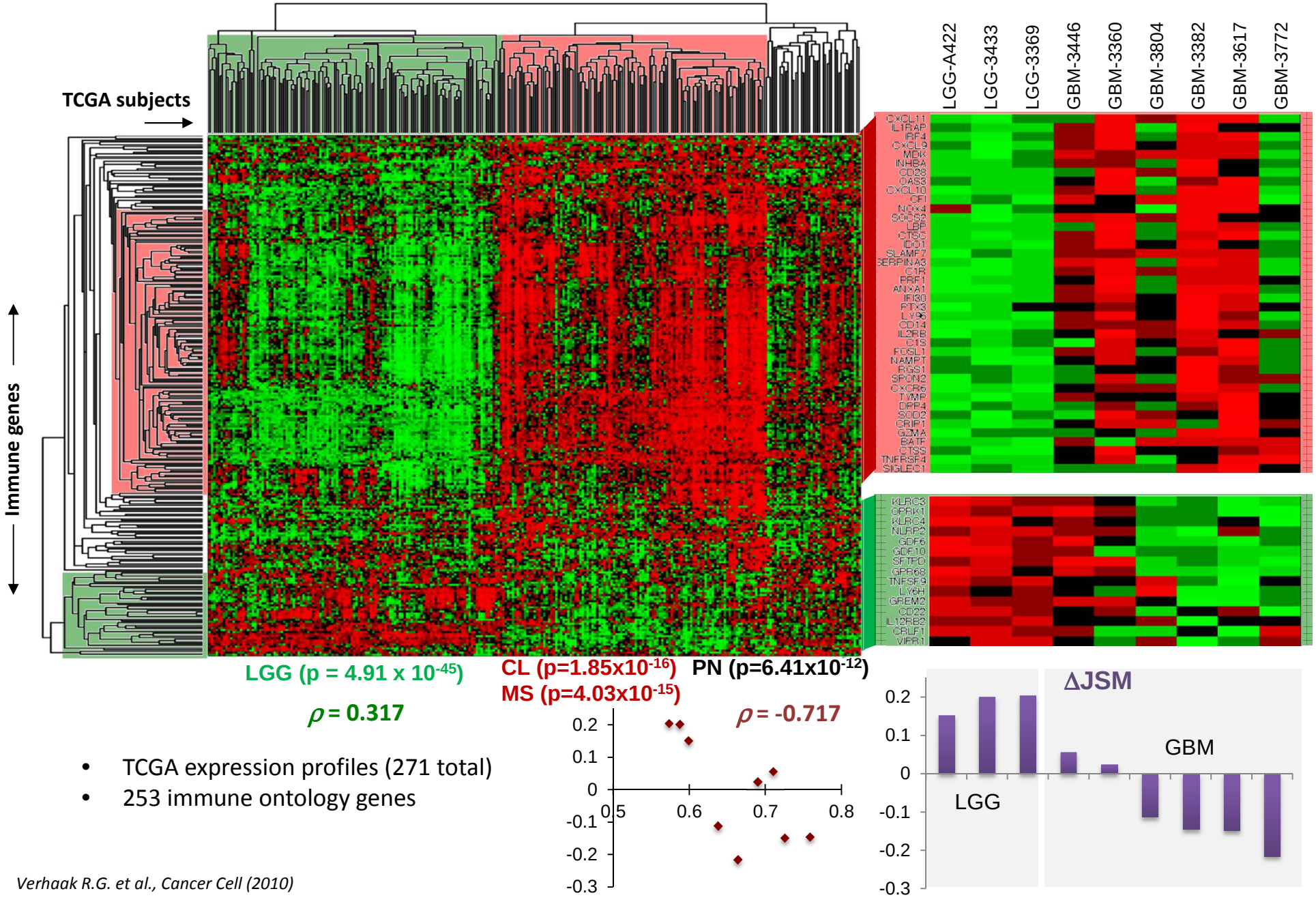


DIVERGENCE OF GLIOMA-INFILTRATING TCRs



Do features of the glioma microenvironment correspond to the TCR divergence phenotype?

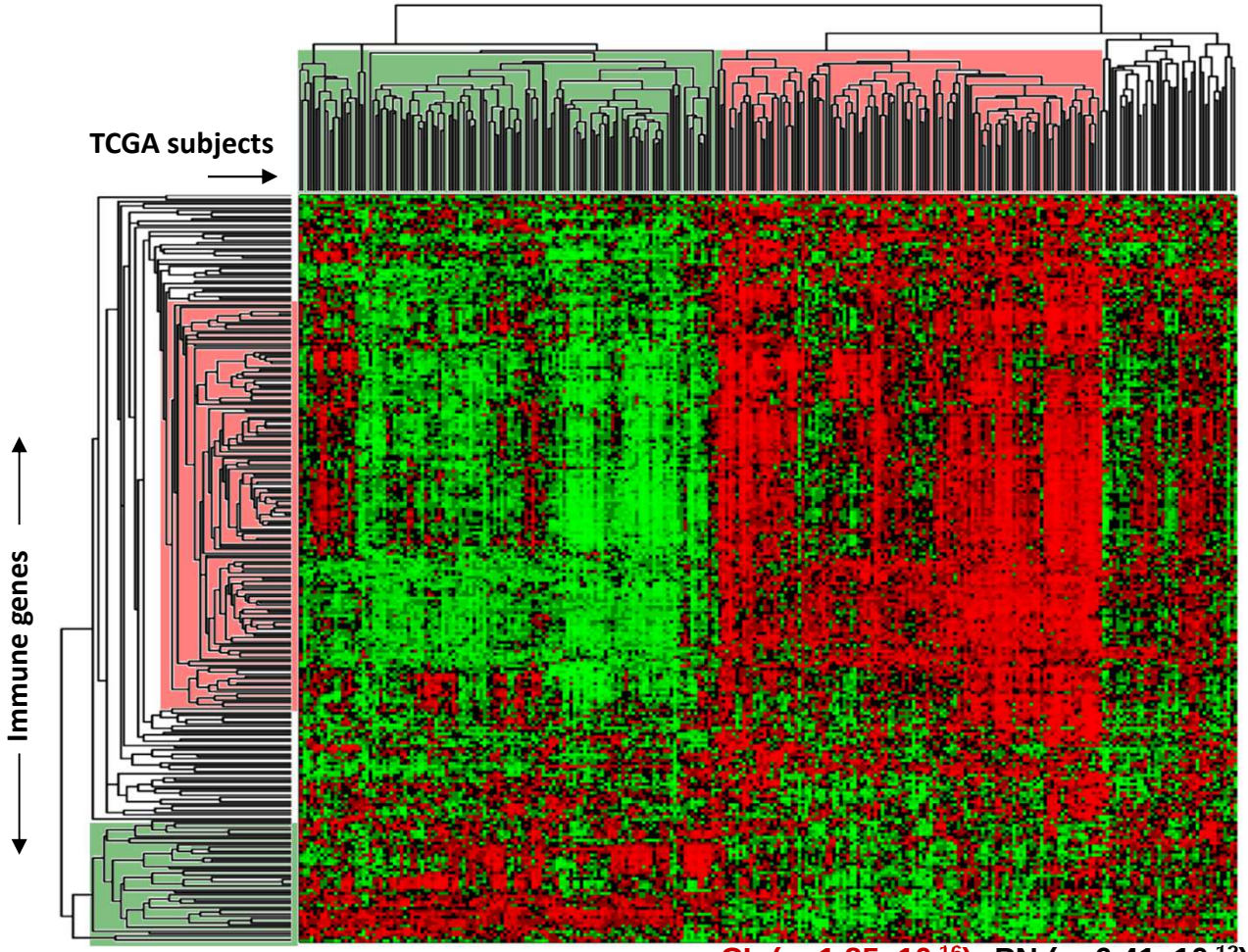
ΔJSM vs. IMMUNE GENE EXPRESSION



- TCGA expression profiles (271 total)
- 253 immune ontology genes

Verhaak R.G. et al., Cancer Cell (2010)

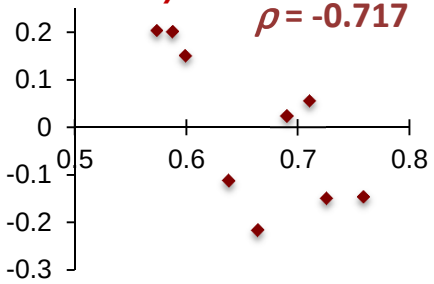
ΔJSM vs. IMMUNE GENE EXPRESSION



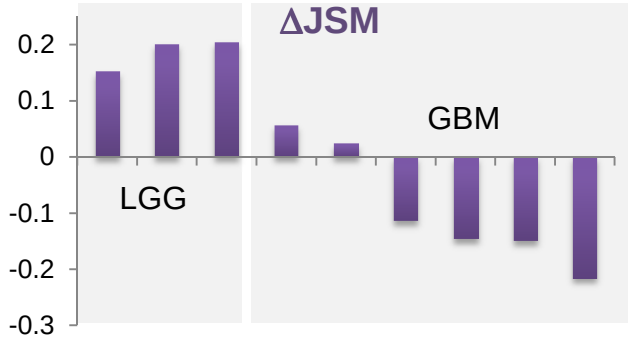
LGG ($p = 4.91 \times 10^{-45}$)

$\rho = 0.317$

CL ($p=1.85\times10^{-16}$) PN ($p=6.41\times10^{-12}$)
MS ($p=4.03\times10^{-15}$)



		Correl. vs ΔJSM (spear.)
Inflammation & stress-induced	**MDK**	-0.767
	IL1RAP	-0.867
	SERPINA3	-0.633
	OAS3	-0.683
Complement pathway	**CFI**	-0.667
	C1R	-0.633
IFN-g induced T cell recruitment & activation markers	**CXCL9**	-0.817
	CXCL10	-0.683
	CXCL11	-0.883
	PRF1	-0.617
	CD28	-0.683
Monocyte markers, activation & survival	CTSC, IDO1, LBP,HLAs	
Lymphocyte recruitment & Th1 maturation	VIPR1	**0.900**
	IL12RB2	**0.800**
	TNFSF9	**0.700**
Inflammation suppression & neuron survival	SFTPD	**0.633**
	GREM2	**0.750**
	CD22	**0.783**
	CRLF1	**0.850**
Modulation of cell stress responses	OPRK1	**0.517**
	GPR68	**0.683**
	NLRP2	**0.568**
TGFβ superfamily	GDF6	**0.600**
	GDF10	**0.617**



- TCGA expression profiles (271 total)
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Verhaak R.G. et al., Cancer Cell (2010)

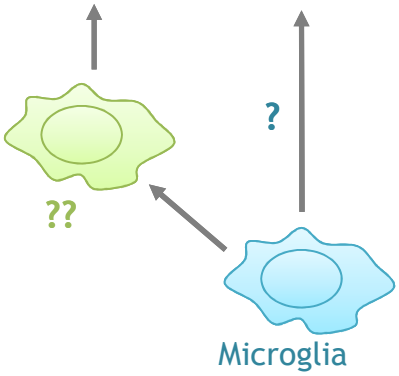
↓ CL_{VJ}
↓ $CL_{totCDR3}$

ΔJSM

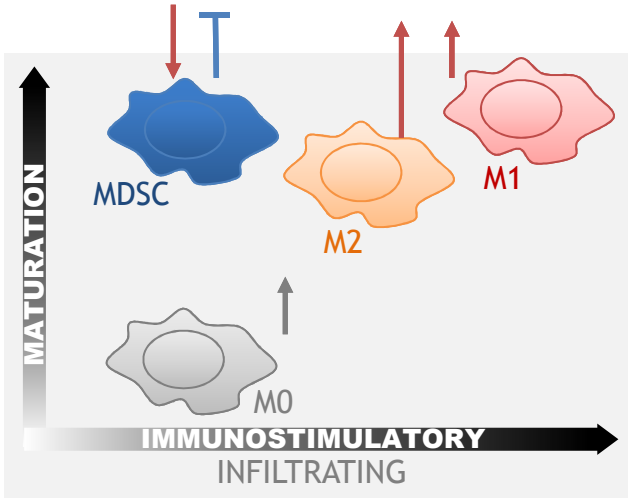
- **LYMPHOCYTE** recruitment & activation
- Inflammation **SUPPRESSION**
- **MODULATION** of cell stress
- **TGFβ & GROWTH FACTOR** signaling

- **MONOCYTE** recruitment, variable activation, survival
- **IFNγ-INDUCED** LYMPHOCYTE recruitment
- Inflammation **INDUCTION**
- **RESPONSE** to cell stress
- **COMPLEMENT** activation

↓~CL

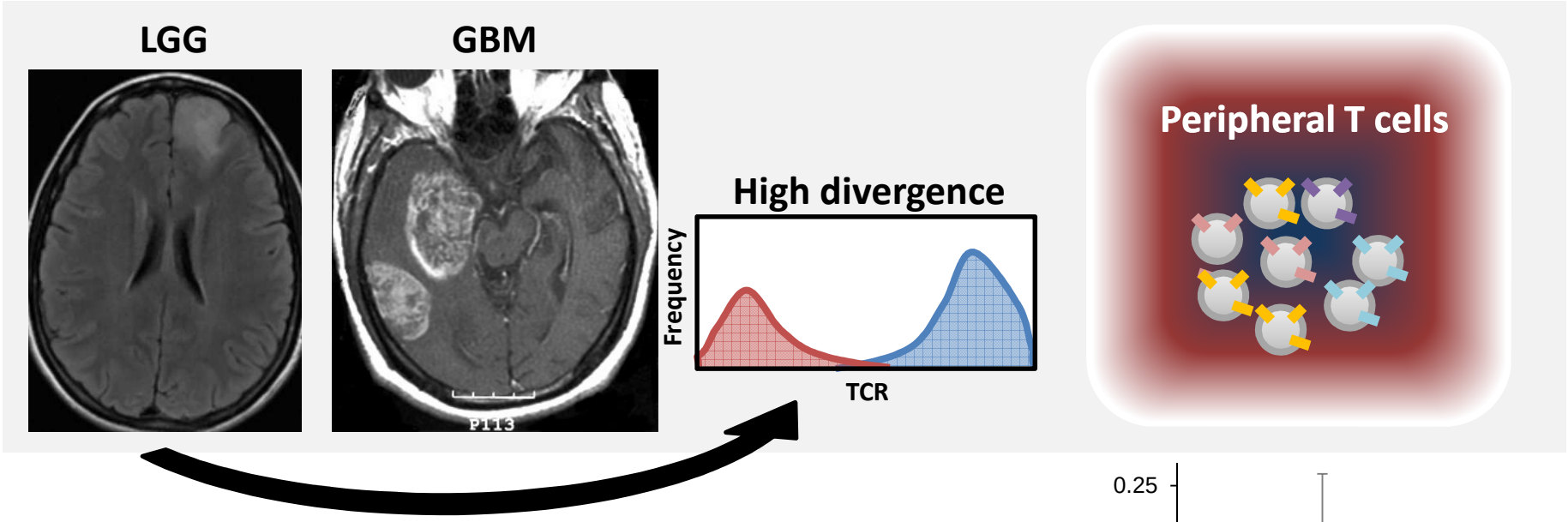


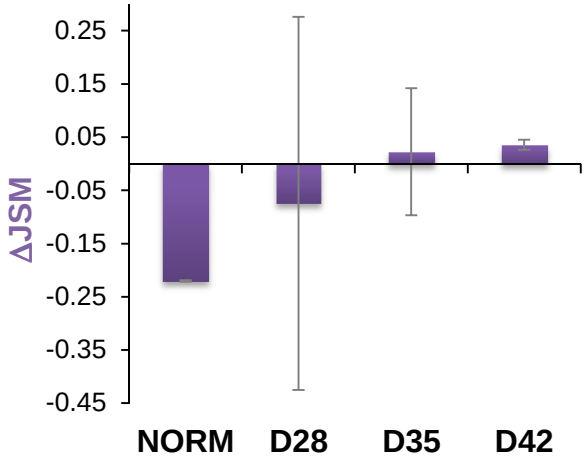
RESIDENT

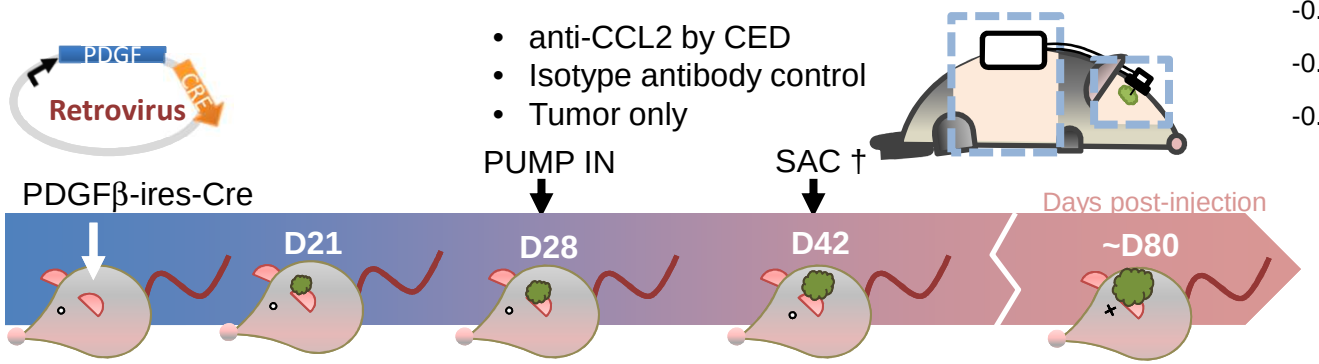


INFILTRATING

Can we manipulate TCR divergence?



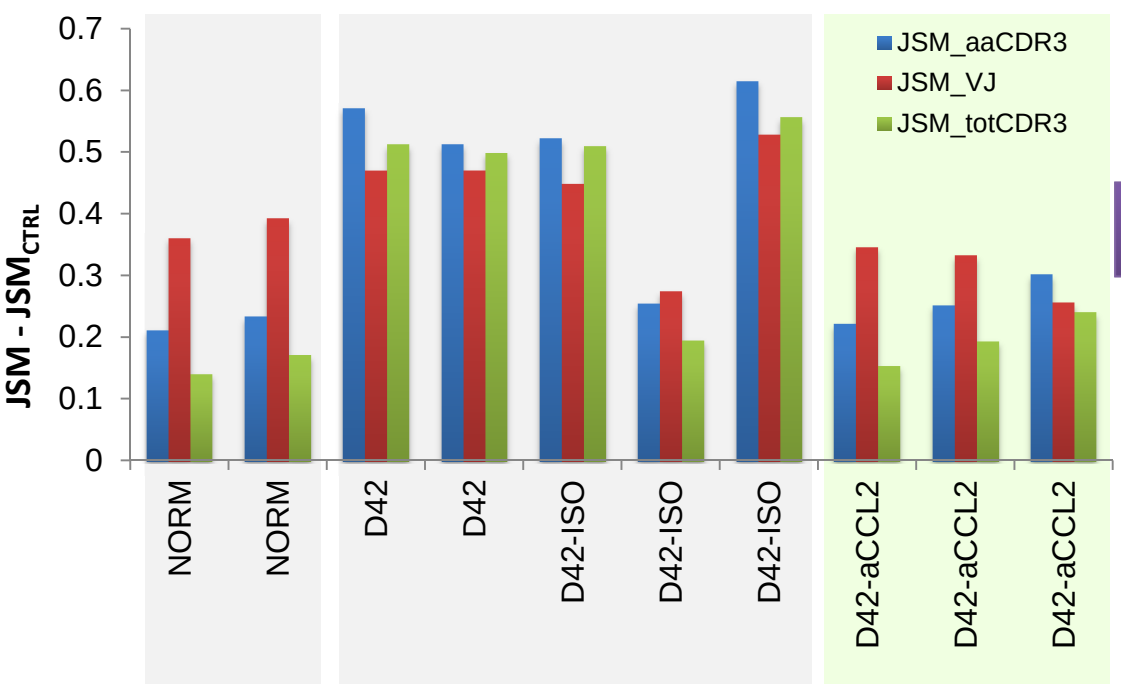


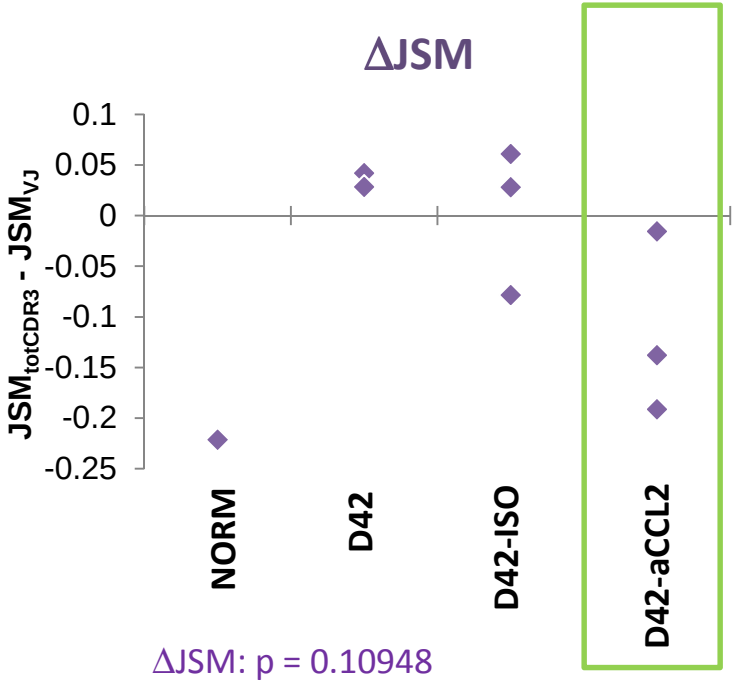


Lei et al., 2010

- **PDGF-driven**
- ***de novo* (retroviral)**
- **Reproducible timing with "low grade" window**

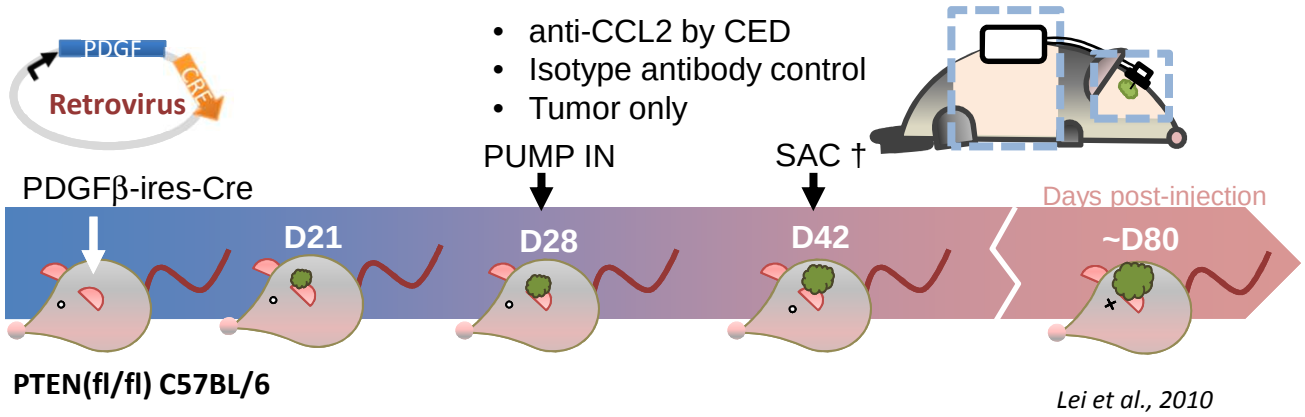
ΔJSM FOLLOWING ANTI-CCL2 IN LOW GRADE





ΔJSM: p = 0.10948

JSM$_{aaCDR3}$: p = 0.01406



Lei et al., 2010

- **PDGF-driven**
- ***de novo* (retroviral)**
- **Reproducible timing with "low grade" window**

SUMMARY

Integrating **aaCDR3** and **V-J cassette** information from paired-end long-read TCRseq:

- entropy, clonality, divergence of populations
- gives rise to metrics which implicate modes of population selection, such as

$$\Delta JSM = (JSM_{totCDR3} - JSM_{VJ})$$

LGG: - High brain-blood **ΔJSM**

GBM: - variable brain-blood $\mathbf{JSM_{totCDR3}}$
- variable brain-blood **ΔJSM**

Brain-blood **ΔJSM** in our glioma patients is anti-correlated with the expression of genes involved in the **inflammatory response**, but correlated with the expression of other **monocyte and microglial genes** involved in microenvironmental immune functions

Local, long-term CED of **anti-CCL2** to glioma gave rise to lower brain-blood **ΔJSM** than controls, suggesting dependency on CCL2-mediated activation of antigen presenting cells

TIL vs. peripheral TCR divergence as a functional readout:

- can distinguish **immune states** of the tumor microenvironment
- **variable** between human subjects
- **dynamic** over time in the mouse model
- potential metric for **personalized** immunotherapy

THANK YOU

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