Efficacy Through Diversity: The Role of HLA Polymorphism in Response to Checkpoint Blockade Immunotherapy

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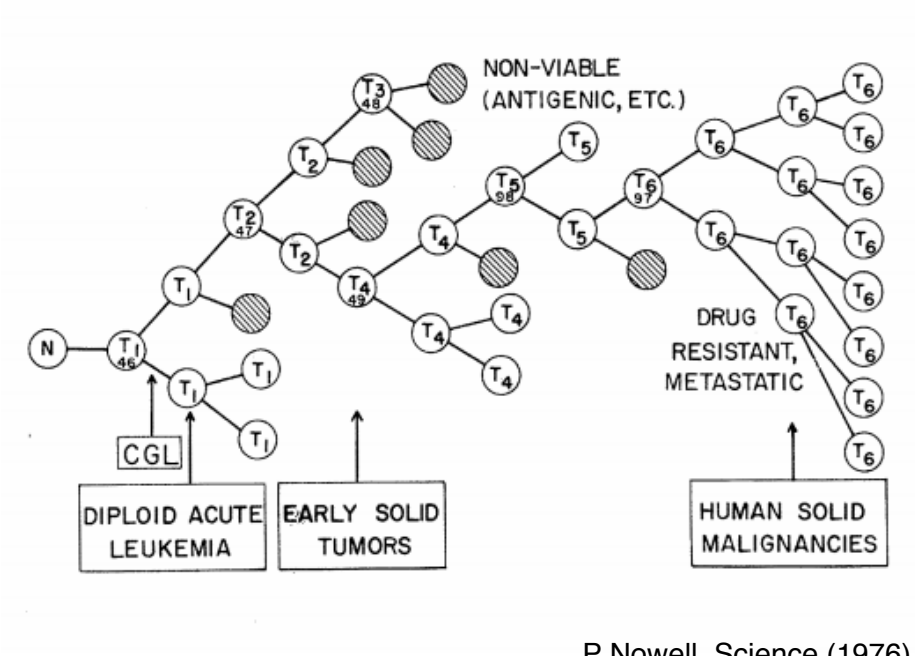
Cancer Immune Responsiveness Workshop
Session I: Germline Genetic Contributions to Immune Landscape
San Francisco, May 14, 2018

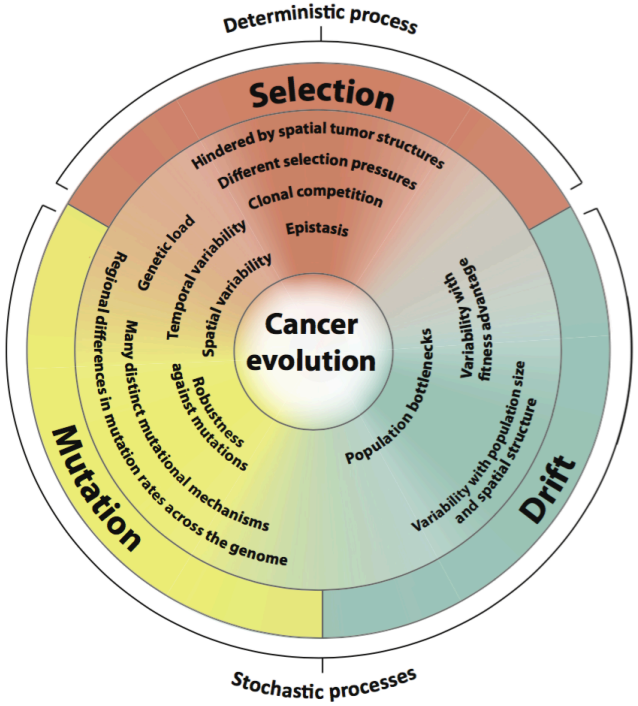
Outline

- Background
- The role of neoantigens in recognizing a cancer as foreign
- Evidence for tumor mutational burden and response to immune checkpoint blockade (ICB)
- The role of germline HLA class I in immune recognition
- Germline HLA class I influences response to ICB
- Summary

Cancer is a genetic disease

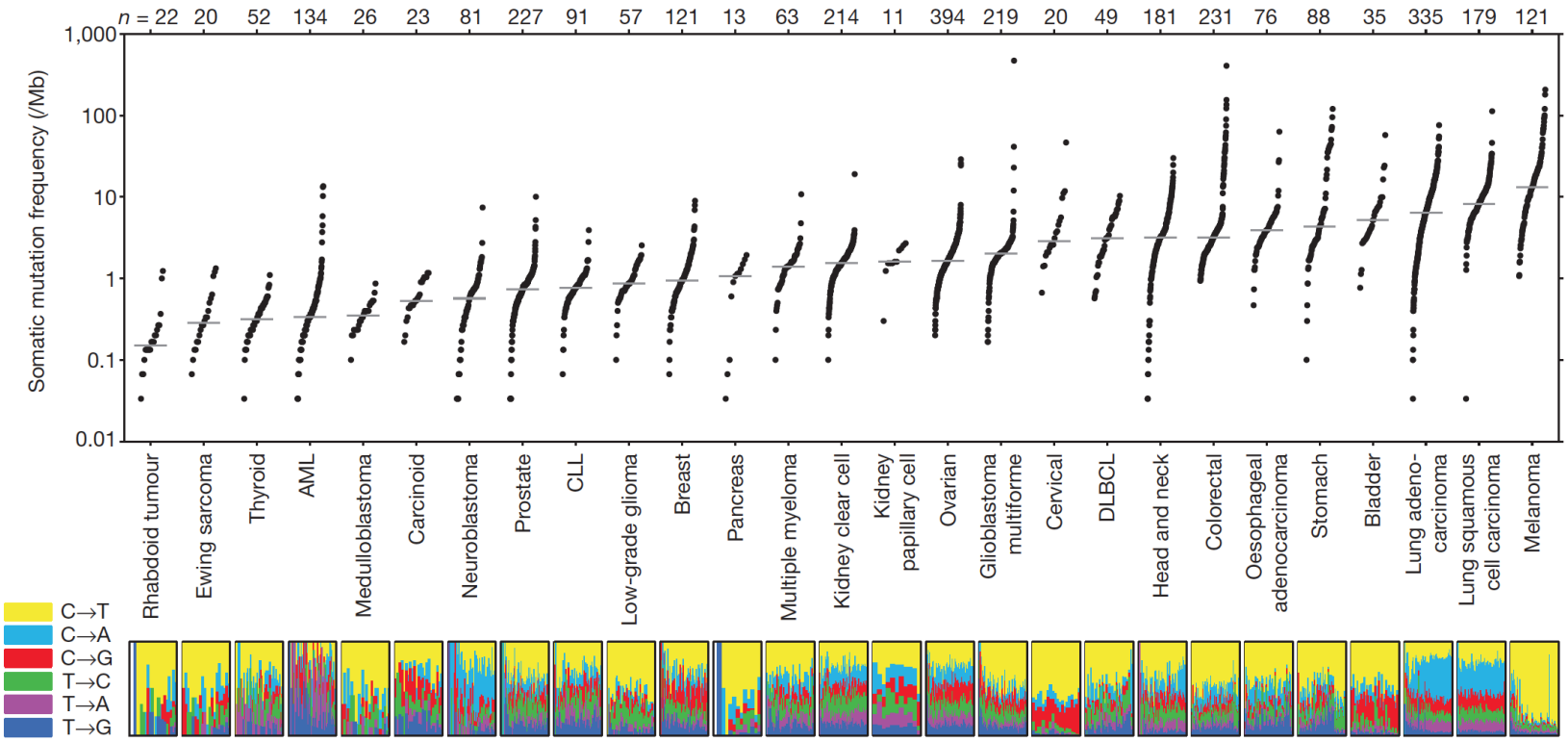


P Nowell. Science (1976)



K Lipinski et al. Cell Trends in Cancer (2016)

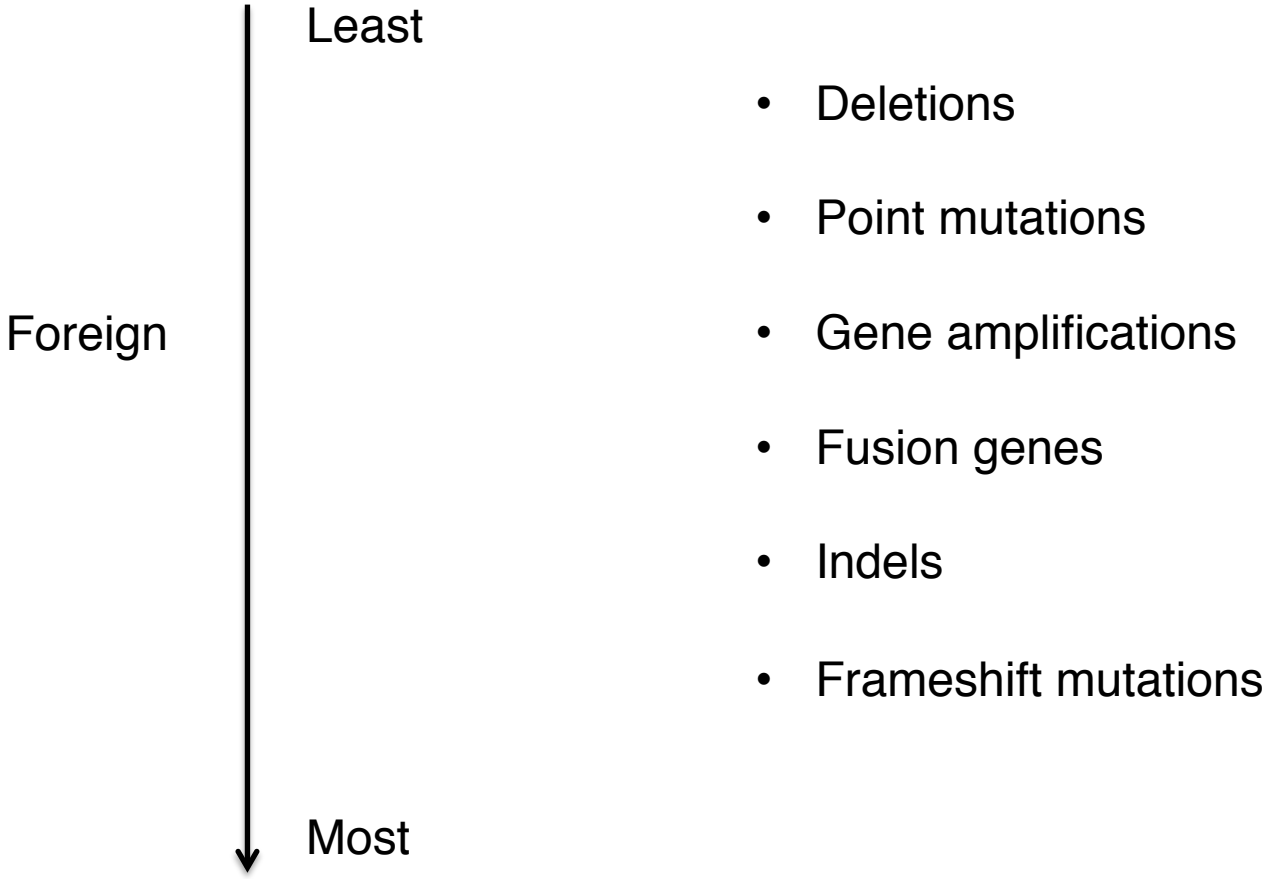
Mutational heterogeneity in cancer



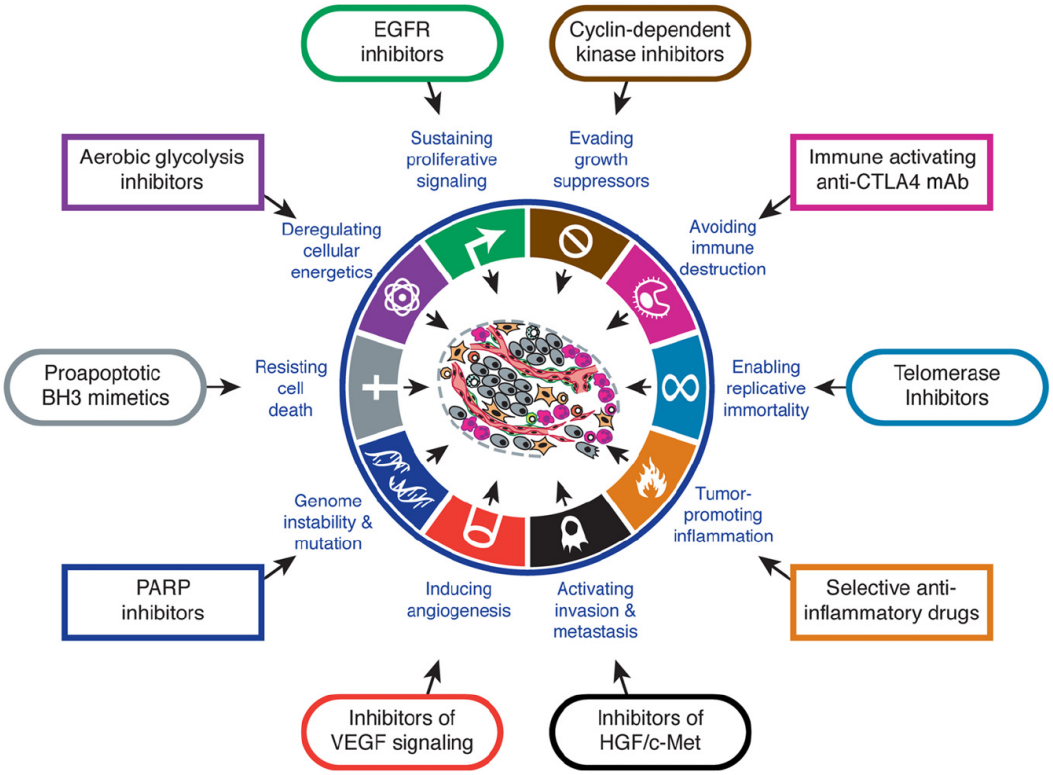
MS Lawrence et al. Nature (2013)

Mutational heterogeneity in a tumor creates new proteins that can potentially be recognized by the immune system, and provides a common denominator for immunotherapy

Different genomic alterations can create immunogenic neoantigens



Avoiding immune destruction is a hallmark of cancer



D Hanahan and R Weinberg. Cell (2011)

Targeting the immune system: Immune checkpoint blockade (ICB)

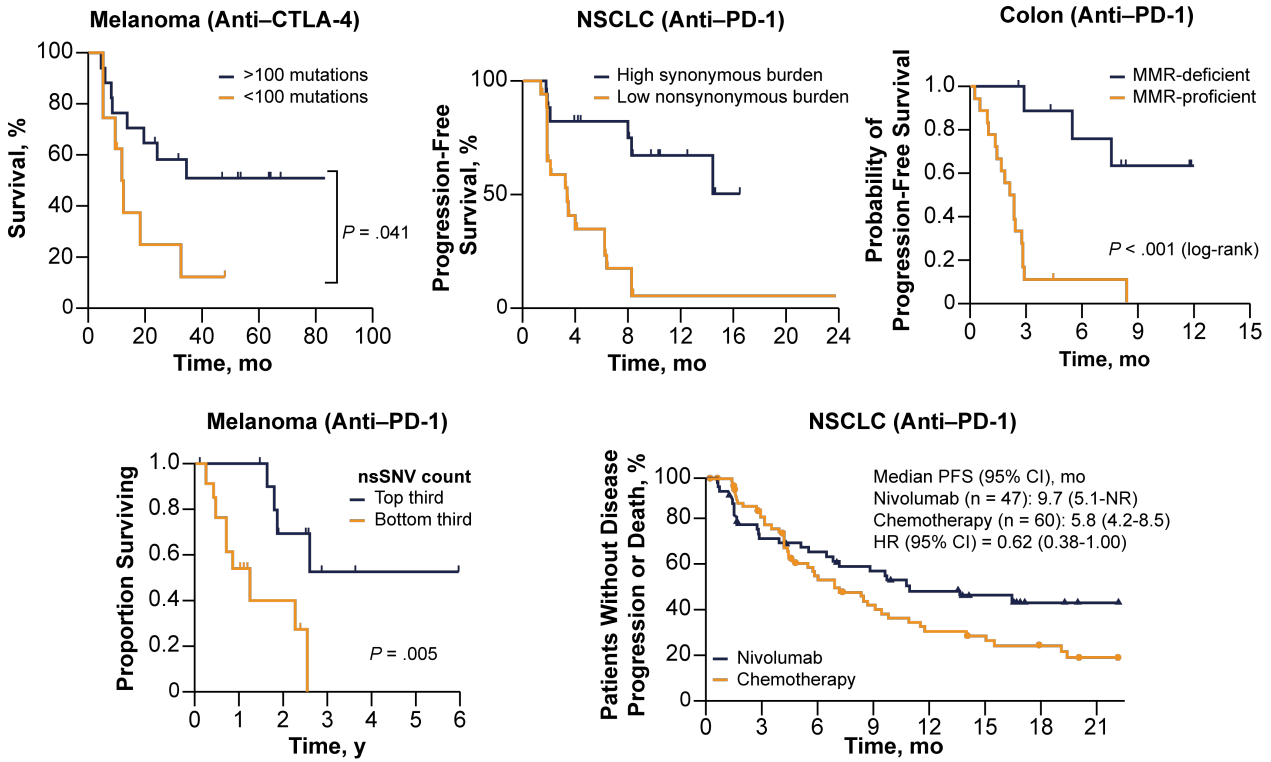
Checkpoint Inhibitors (PD-1/PD-L1) Have Opened Up Exciting New Treatment Pathways

…but the vast majority of patients have continued unmet medical need!

	Indication	ORR (%)	No Response (%)
APPROVED	**Melanoma**	33.7	**66.3**
APPROVED	**NSCLC**	19.2	**80.8**
APPROVED	**RCC**	25.0	**75.0**
APPROVED	**Bladder Ca.**	14.8	**85.2**
	Gastric	30.0	**70.0**
	Pancreatic Ca.	17.0	**83.0**

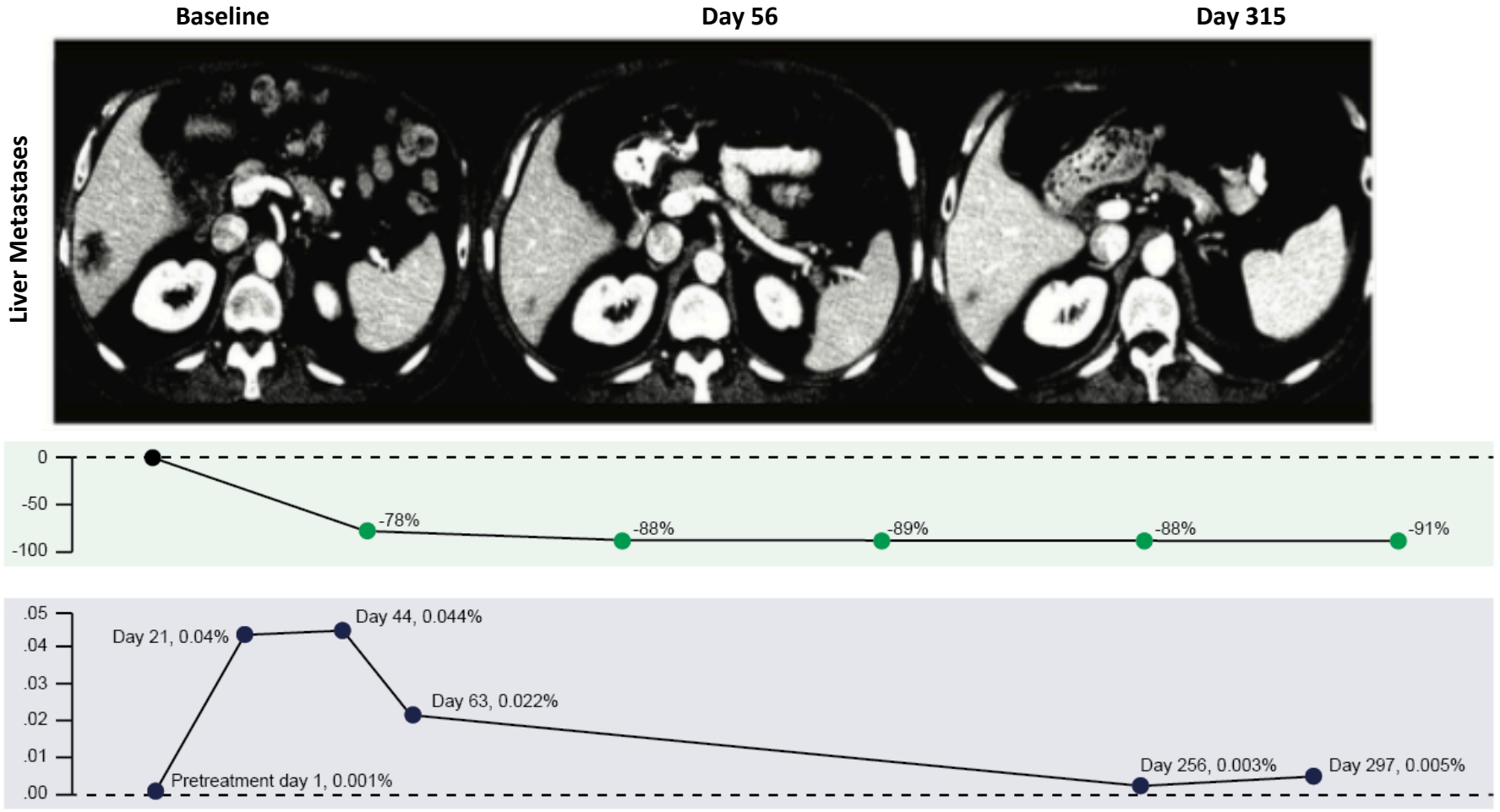
The role of mutation load in response to immune checkpoint blockade

- An elevated number of mutations increases the probaility that a tumor will be recognized as foreign via presentation of neoantigens



1. Snyder A et al. *N Engl J Med*. 2014;371:2189-2199. 2. Rizvi NA et al. *Science*. 2015;348:124-128. 3. Le DT et al. *N Engl J Med*. 2015;372:2509-2520. 4. Van Allen EM et al. *Science*. 2015;350:207-211. 5. Hugo W et al. *Cell*. 2016;165:35-44. 6. Carbone DP et al. *N Engl J Med*. 2017;376:2415-2426.

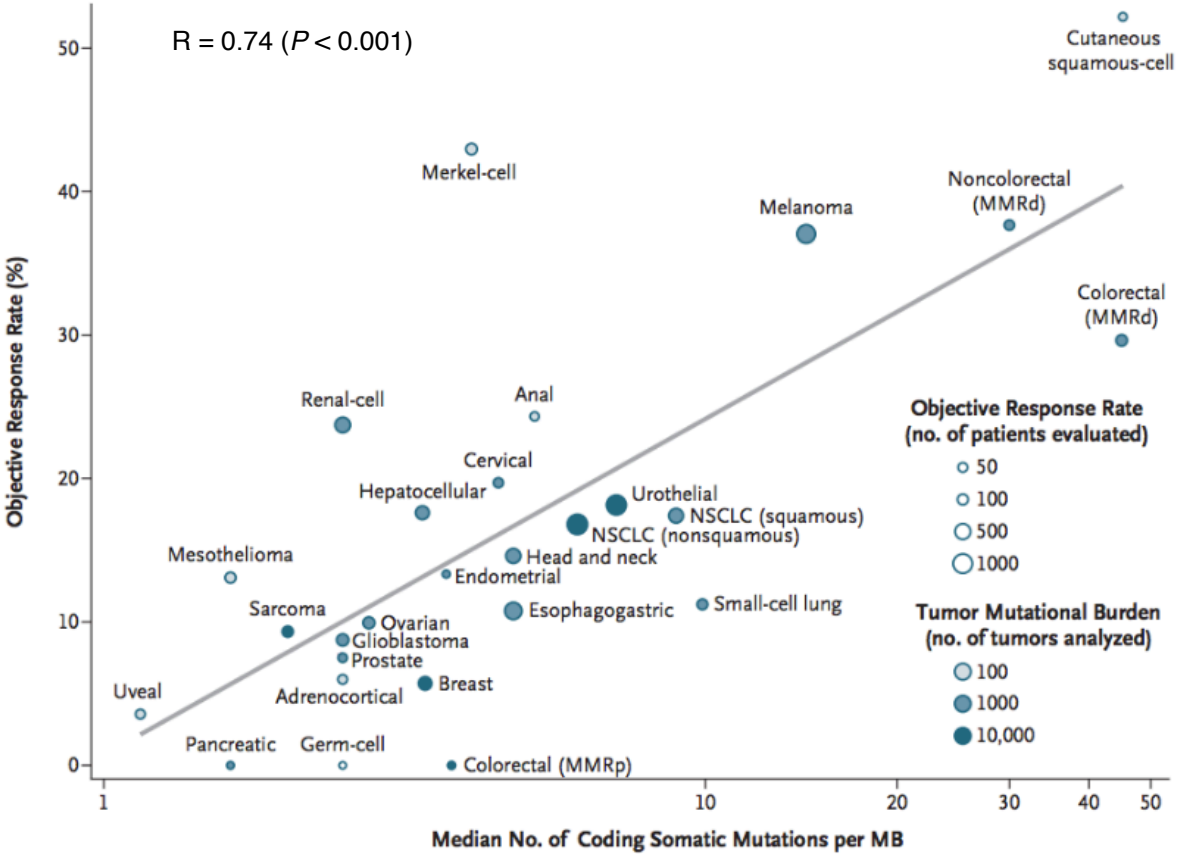
CD8+ T-cell targeting a neoepitope expands with response



WT: ASNAPSAAK MUT: ASNASSAAK presented by HLA-A*11:01

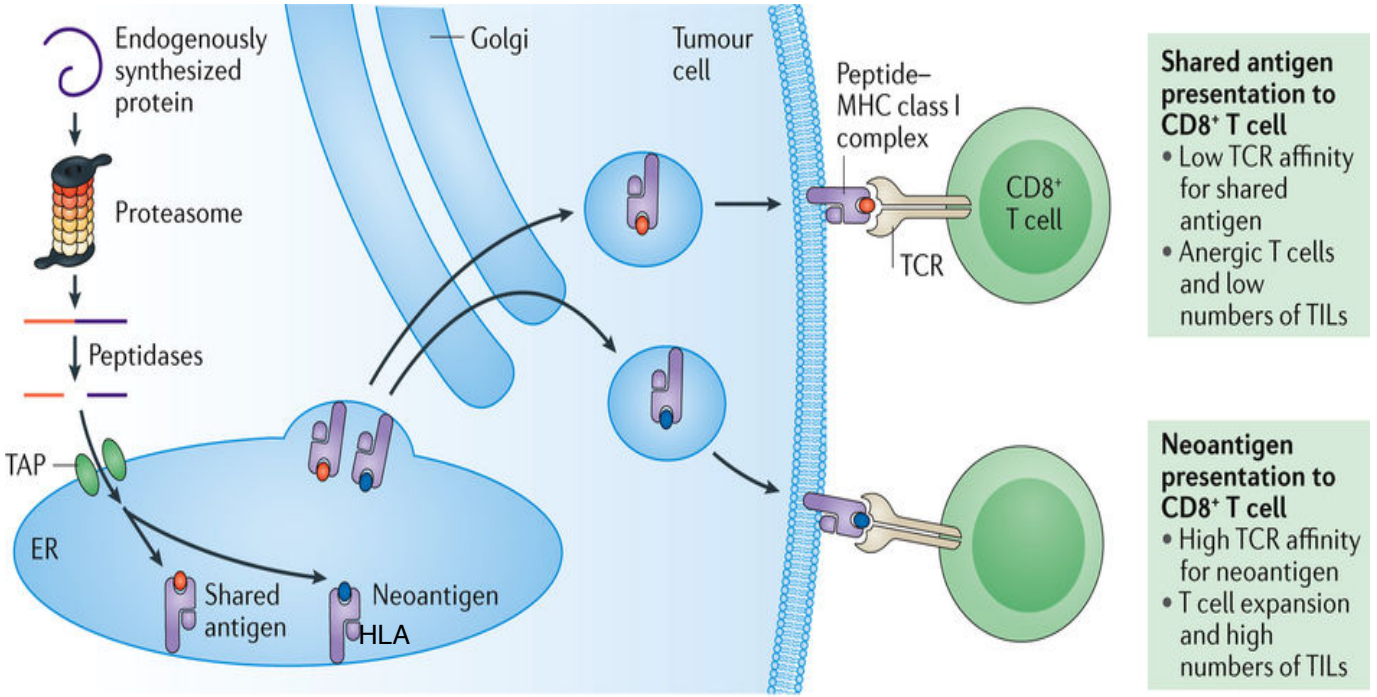
Rizvi et al. Science 2015

Response rates across cancer types correlate with tumor mutation load

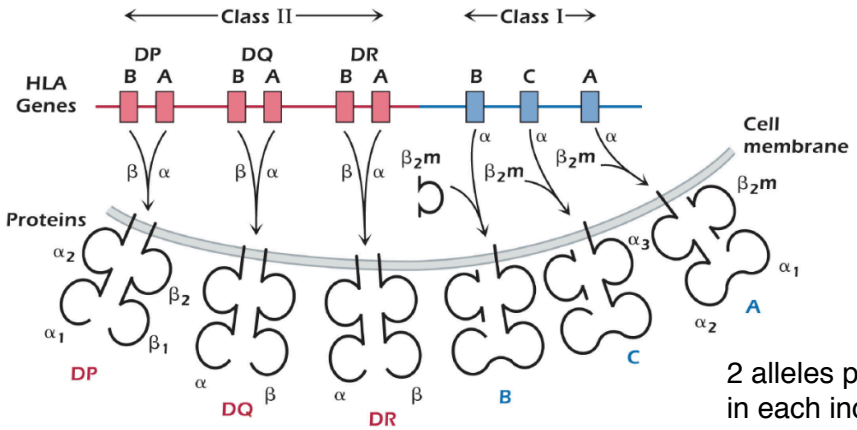


M Yarchoan et al. NEJM (2017)

How does the immune system recognize neoantigens?



Yarchoan et al. Nature Reviews Cancer (2017)



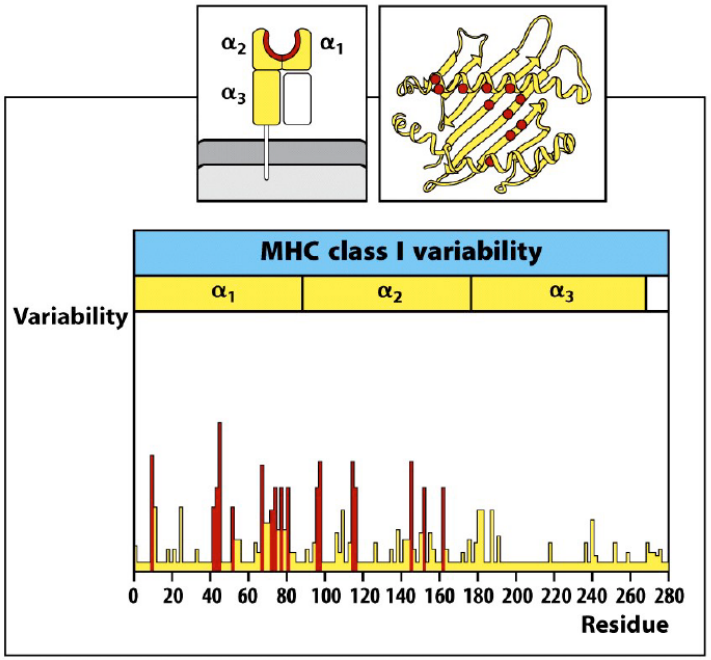
2 alleles per HLA class I locus in each individual

Not all neopeptides presented by HLA-Is can be recognized by T cells

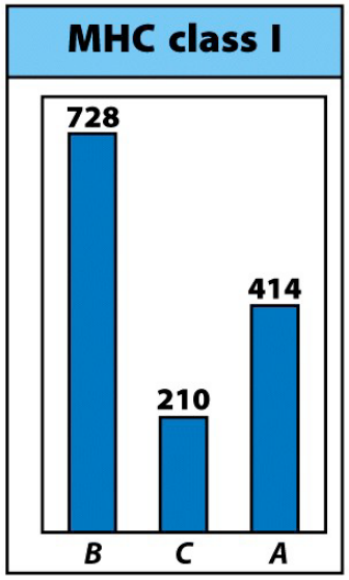
Importance of HLA genetic diversity in a given individual

- Encode the MHC class I and II molecules
- Present self and foreign peptides to adaptive immune system
- HLA diversity is selected for over evolution
- High HLA diversity associated with better resistance against infectious diseases
- Specific HLA genes associated with exceptional resistance or susceptibility to certain pathogens (ie. HIV, malaria, etc.)

HLA class I allele diversity



AL Hughes and M Nei. Nature (1988)

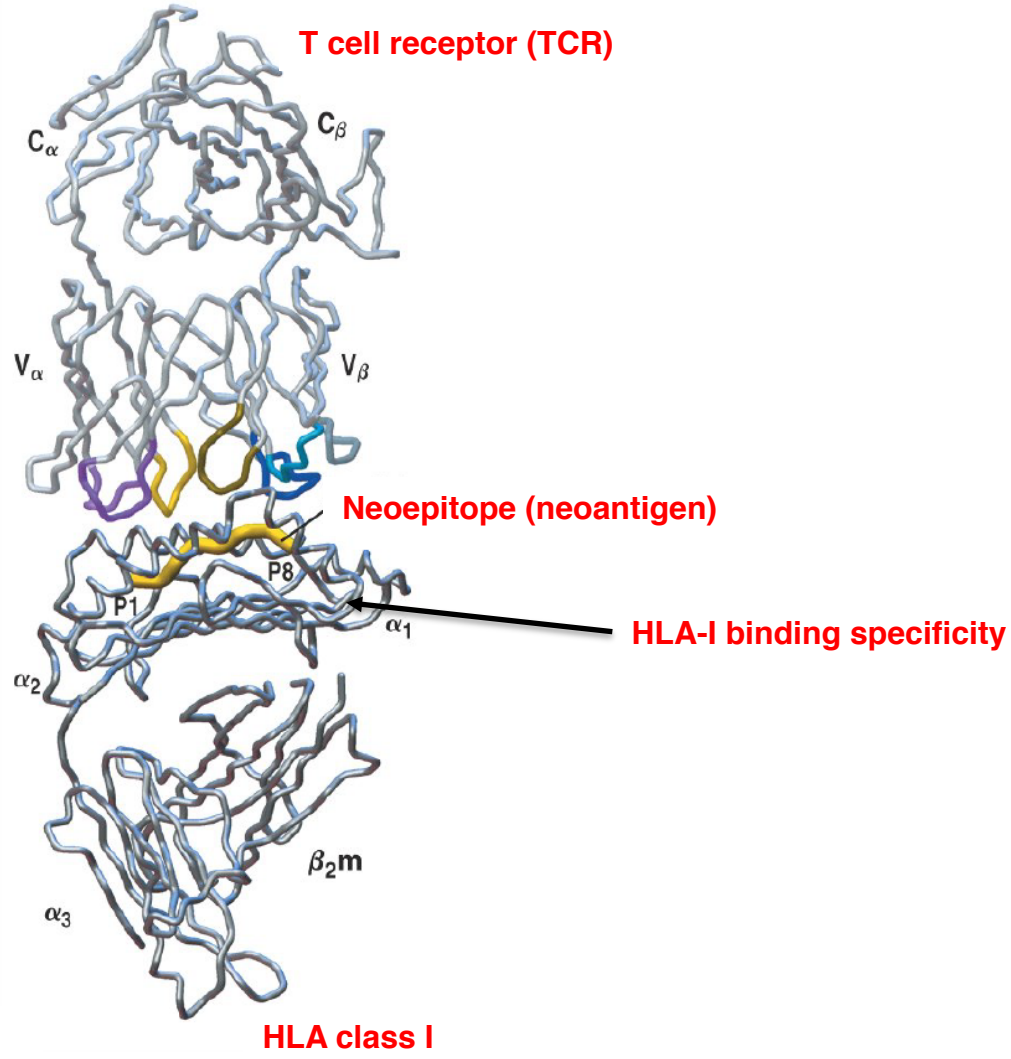


Janeway's Immunobiology (2017)

(as of January 2010)

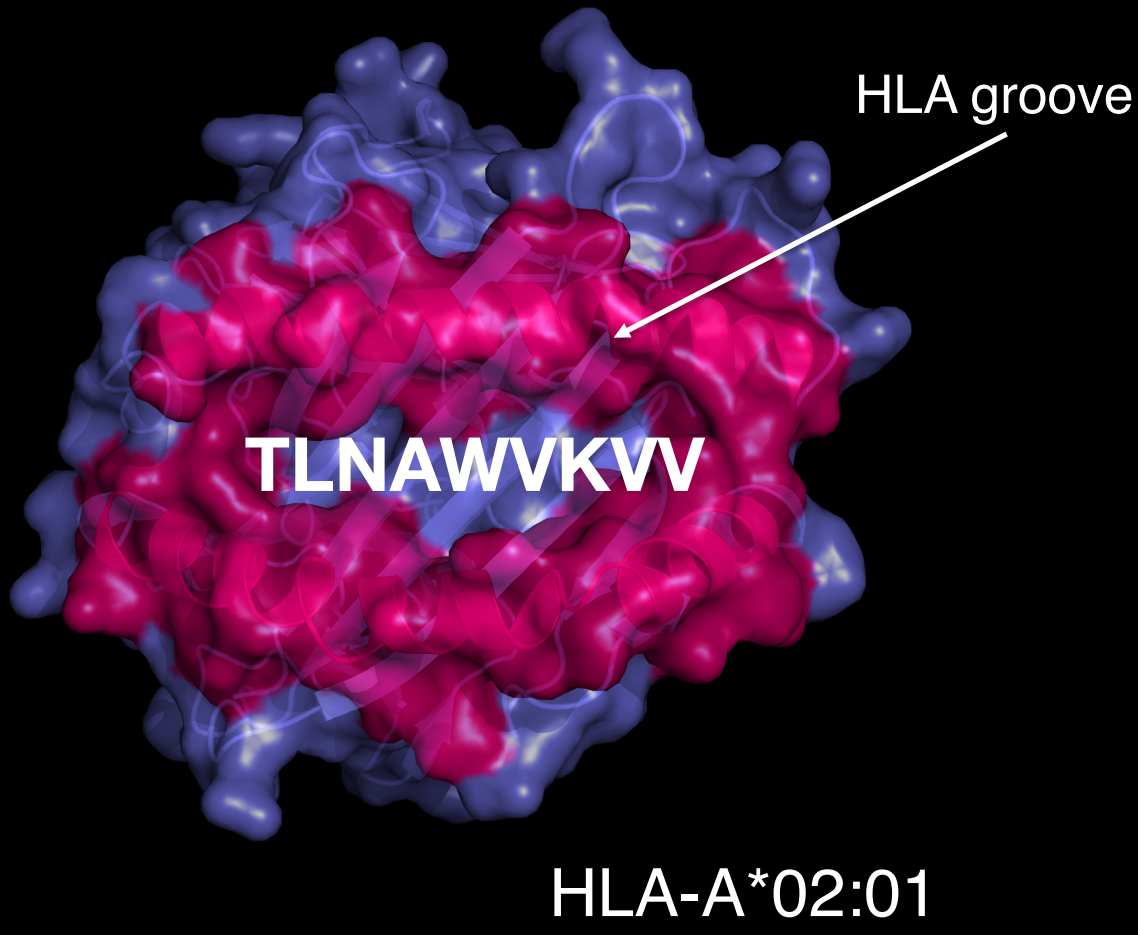
In a given individual, multiple different HLA I alleles results in many different peptides bound (variations in peptide binding groove)

TCR-neoepitope-HLA

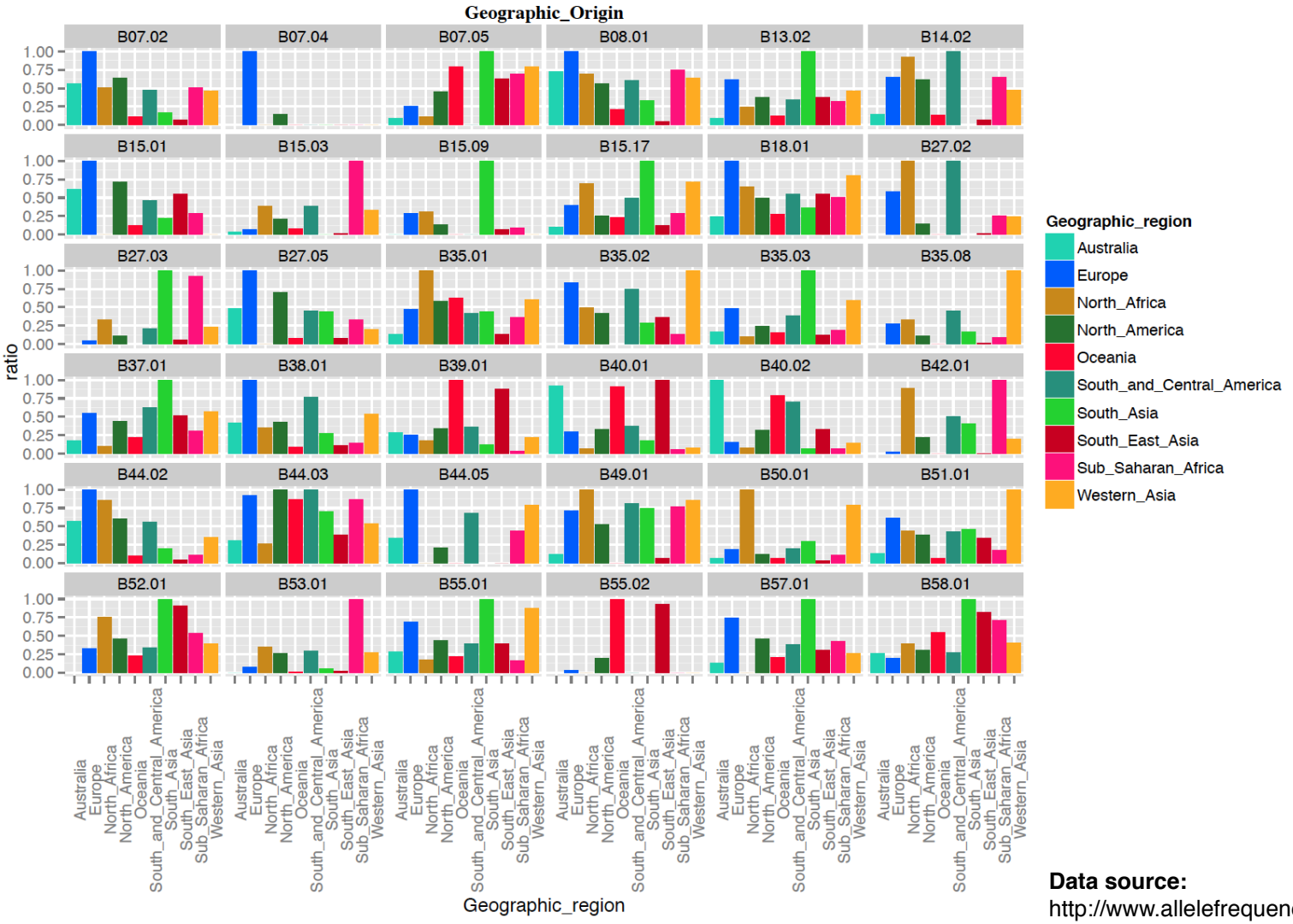


HLA-I polymorphism affects which peptides can bind and be presented to T cells

- Humans have HLA- A, B, C *(polygenic)*
- Many alleles of each HLA locus *(polymorphic)*
- Anchor chains depend on the MHC allele

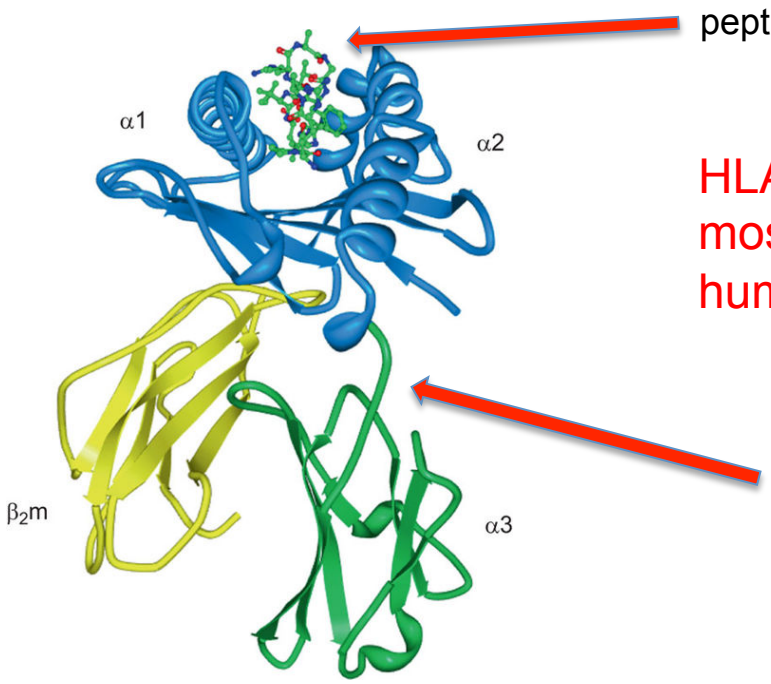


HLA-B allele frequency across geographic regions

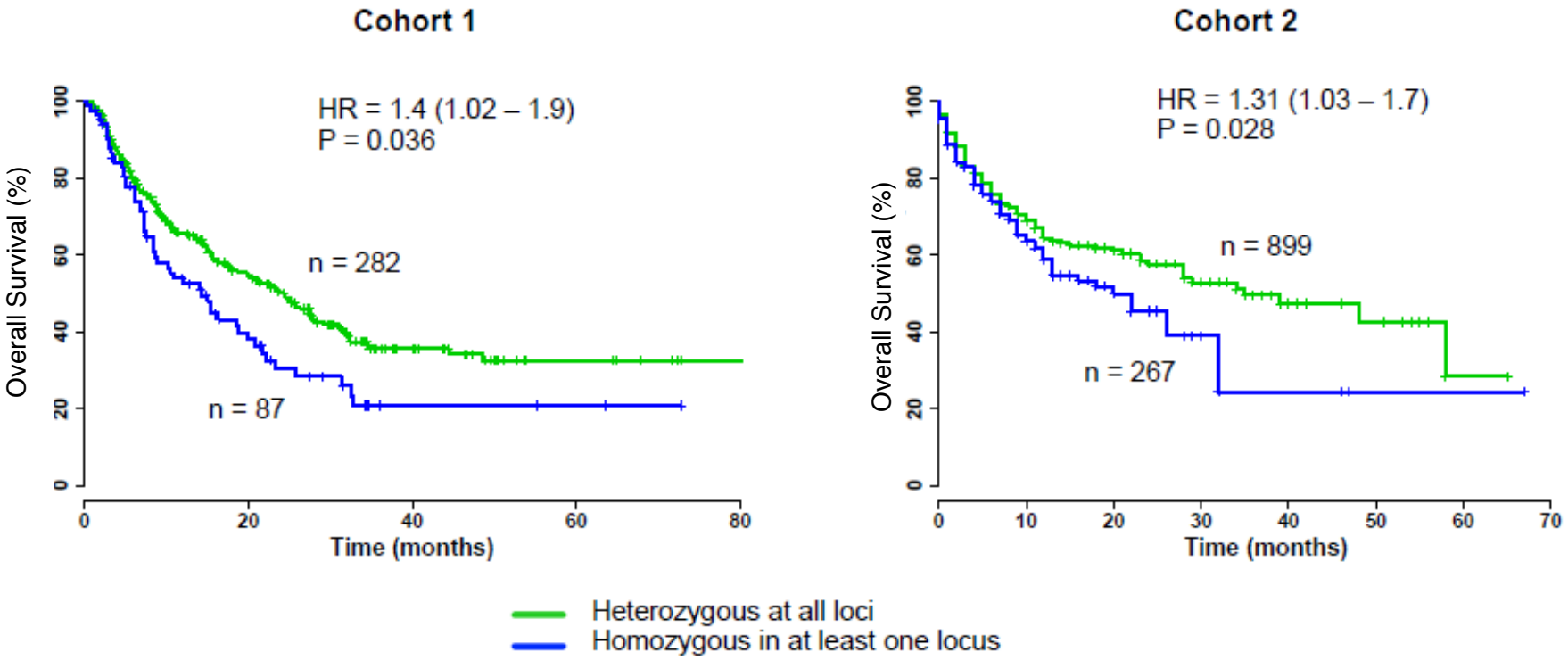


Data source:
http://www.allelefrequencies.net/

Can the Germline HLA Influence Immune Recognition?

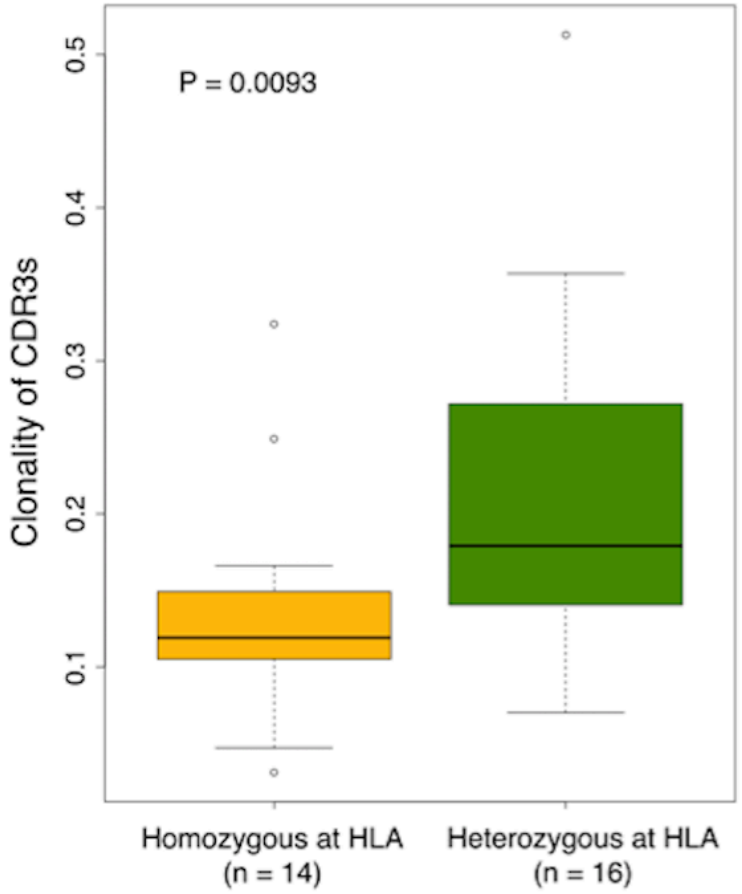


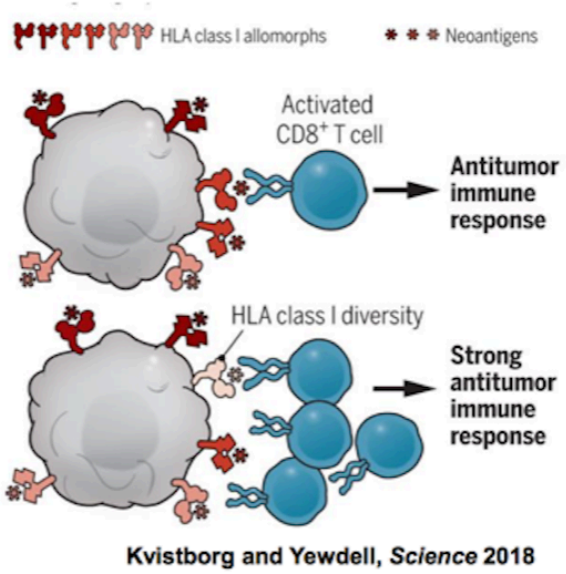
HLA class I heterozygosity associated with improved survival after ICB



D. Chowell et al. Science (2017)

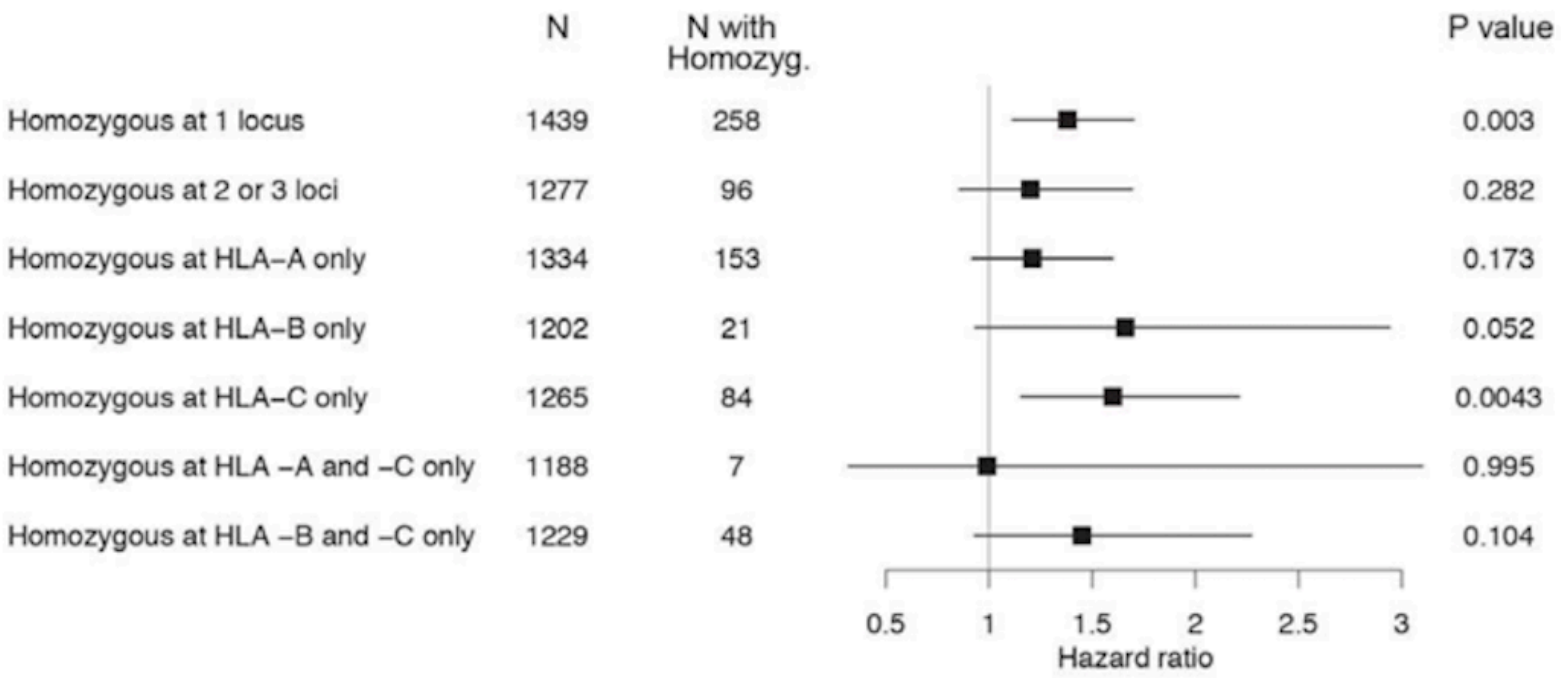
HLA heterozygosity is associated with higher TIL TCR repertoire clonality during PD-1 blockade





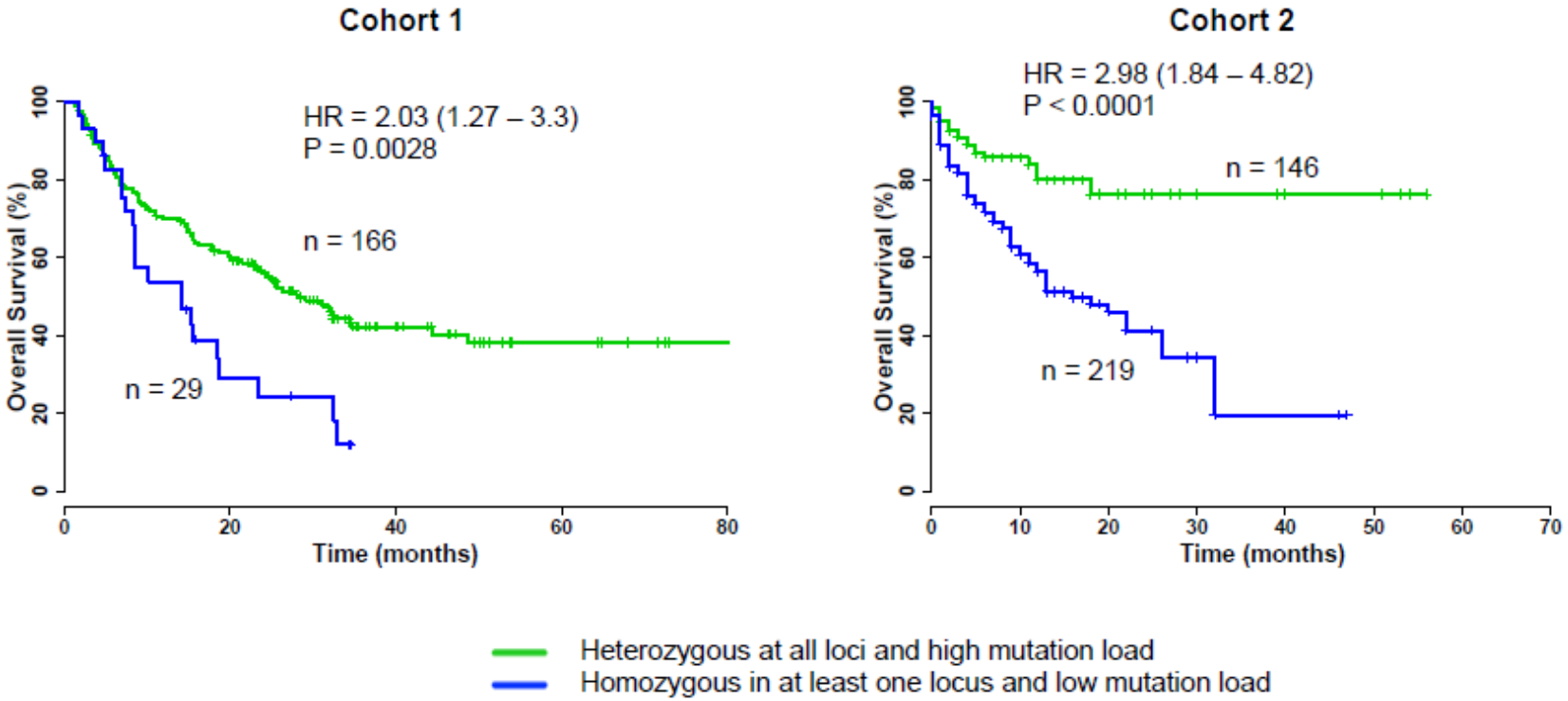
Kvistborg and Yewdell, *Science* 2018

Effect of HLA class I homozygosity in response after ICB



D. Chowell et al. Science (2017)

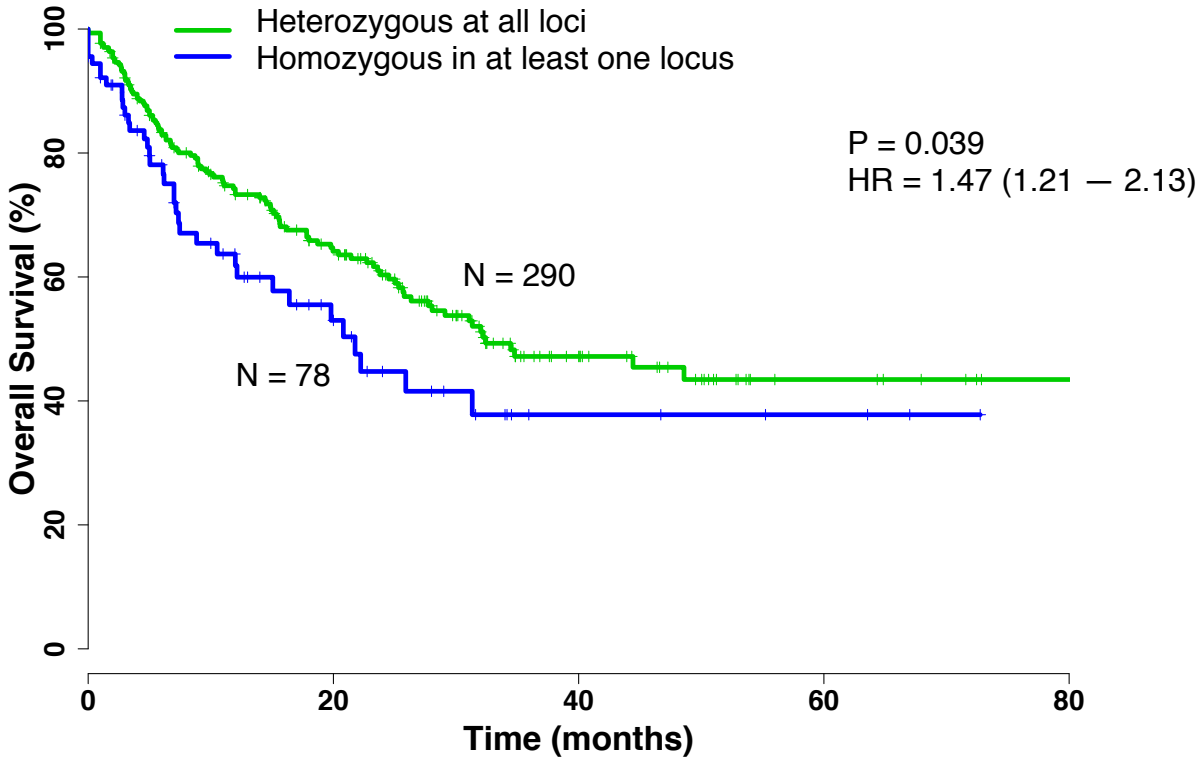
HLA class I zygosity influences impact of tumor mutation load



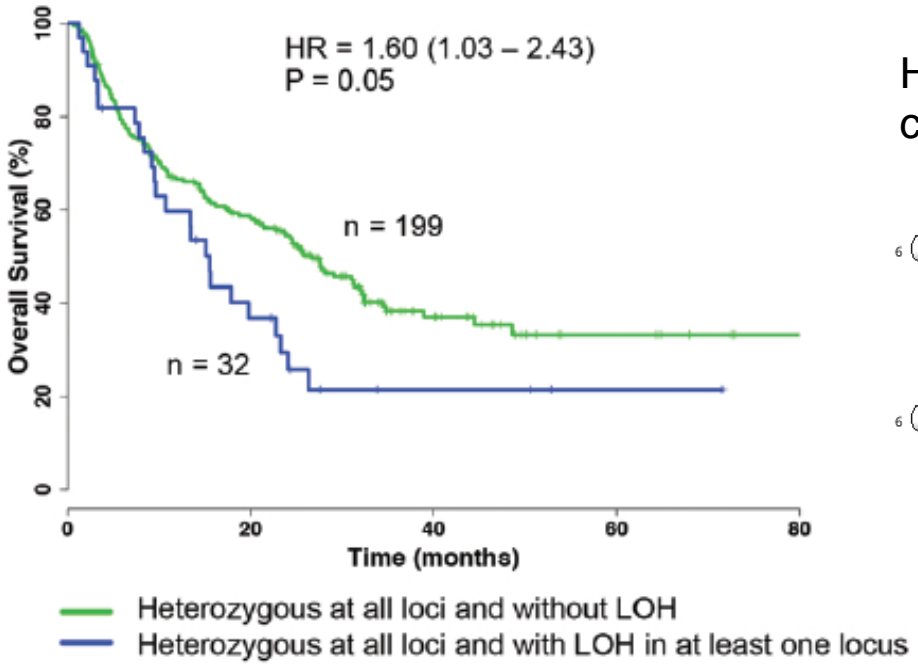
D. Chowell et al. Science 2017

Effect of germline HLA class I zygosity in tumors with only high mutation load

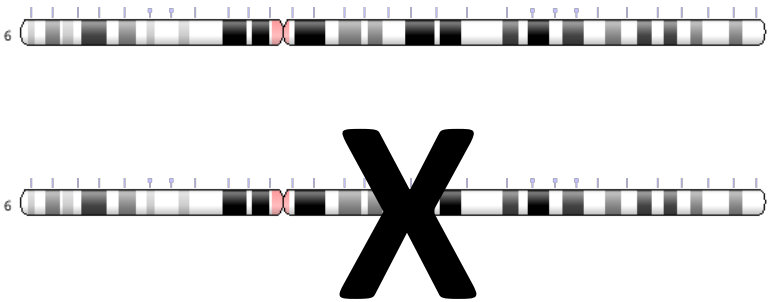
Only tumors with high mutation load are considered here



Somatic LOH of HLA abrogates the benefit of HLA-I germline diversity



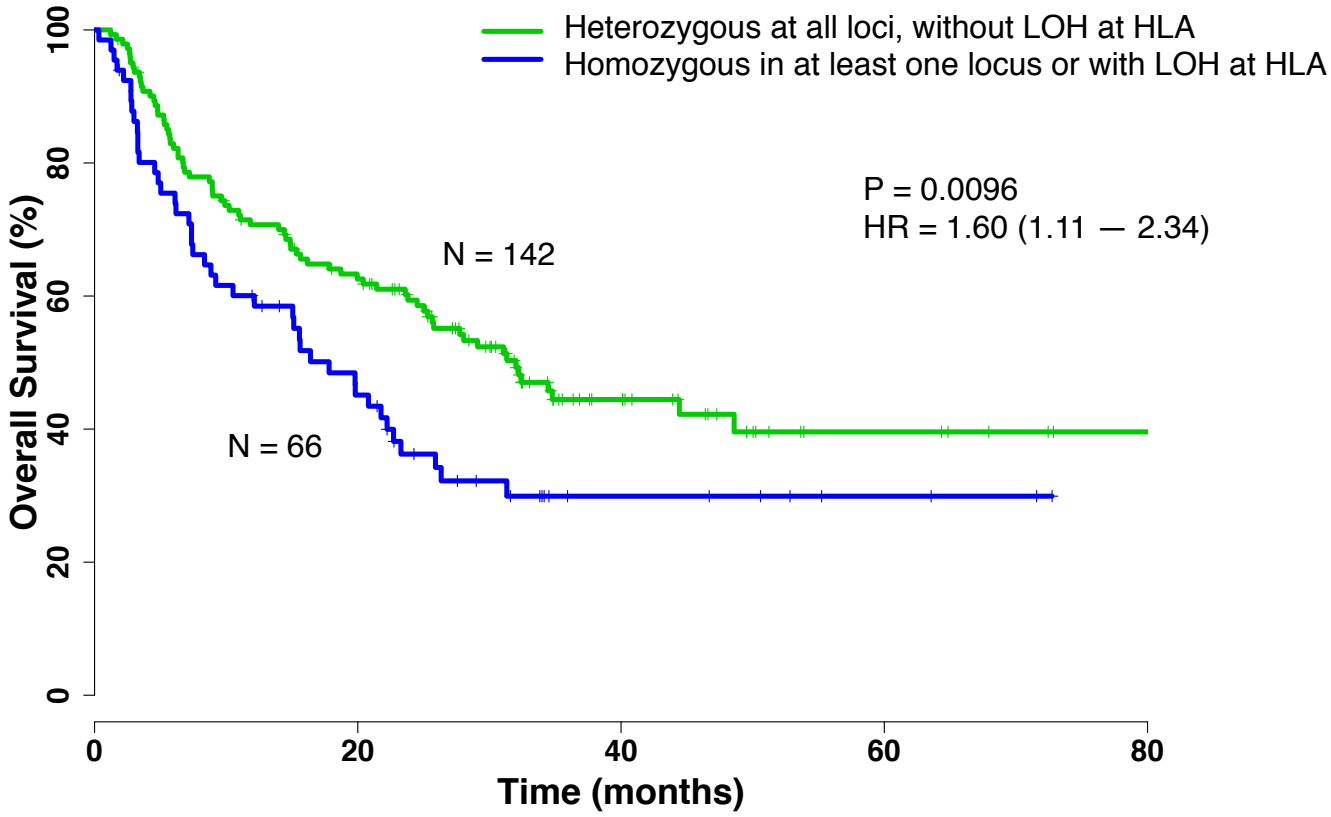
HLA-A, HLA-B, and HLA-C are all on chromosome 6



D. Chowell et al. Science 2017

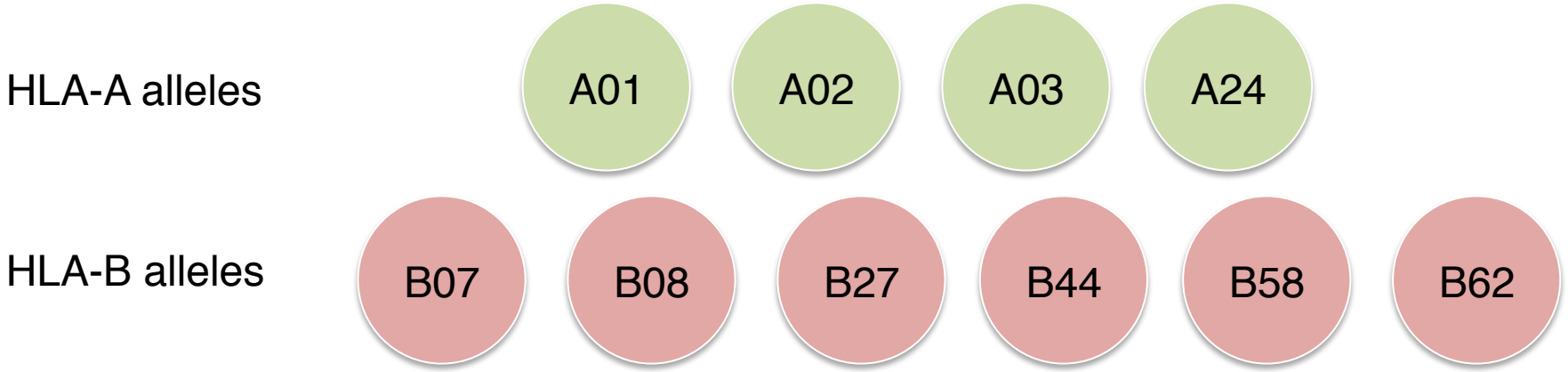
Low HLA-I diversity affects response to ICB in tumors with only high mutation load

Only tumors with high mutation load are considered here



- Only exomes are considered here for the LOH-HLA analysis
- High mutation load is defined as >113 mutations

HLA class I supertypes are defined based on similar peptide-anchor–binding specificities



BMC Immunology

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HLA class I supertypes: a revised and updated classification

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ARTICLES

nature medicine

Advantage of rare HLA supertype in HIV disease progression

Elizabeth Trachtenberg[1,7], Bette Korber[2,3,7], Cristina Sollars[1], Thomas B Kepler[3,4], Peter T Hraber[3], Elizabeth Hayes[1], Robert Funkhouser[2,3], Michael Fugate[2], James Theiler[2], Yen S Hsu[1], Kevin Kunstman[5], Samuel Wu[5], John Phair[5], Henry Erlich[1,6] & Steven Wolinsky[5]

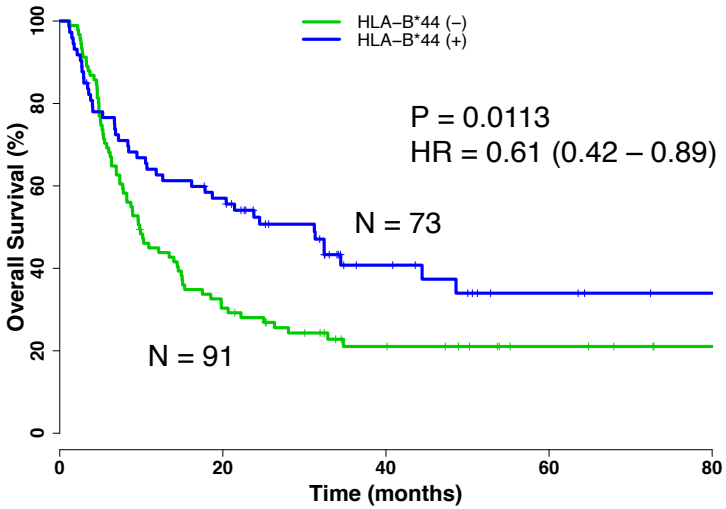
The highly polymorphic human leukocyte antigen (HLA) class I molecules help to determine the specificity and repertoire of the immune response. The great diversity of these antigen-binding molecules confers differential advantages in responding to pathogens, but presents a major obstacle to distinguishing *HLA* allele–specific effects. HLA class I supertypes provide a functional classification for the many different *HLA* alleles that overlap in their peptide-binding specificities. We analyzed the association of these discrete HLA supertypes with HIV disease progression rates in a population of HIV-infected men. We found that HLA supertypes alone and in combination conferred a strong differential advantage in responding to HIV infection, independent of the contribution of single *HLA* alleles that associate with progression of the disease. The correlation of the frequency of the HLA supertypes with viral load suggests that HIV adapts to the most frequent alleles in the population, providing a selective advantage for those individuals who express rare alleles.

Discovery (Cohort 1)

Cohort 1: Patients with melanoma treated with anti-CTLA-4 (N = 164) or anti-PD-1 (N = 105)

1 Identification of B44 supertype associated with increased survival after anti-CTLA-4

2 Identification of specific alleles within the B44 supertype driving this association



European Journal of Immunology

Essential differences in ligand presentation and T cell epitope recognition among HLA molecules of the HLA-B44 supertype

Nina Hillen[1], Gabor Mester[1], Claudia Lemmel[1], Andreas O. Weinzierl[1], Margret Müller[1], Dorothee Wernet[2], Jörg Hennenlotter[3], Arnulf Stenzl[3], Hans-Georg Rammensee[1] and Stefan Stevanović[1,4]

- **Only 3% of ligands are shared between the different B44 members**
- **Even members of the same supertype are expected to present a different peptide repertoire**
- **Therefore, it is imperative to identify specific alleles within the B44 supertype driving the association**

Discovery (Cohort 1)

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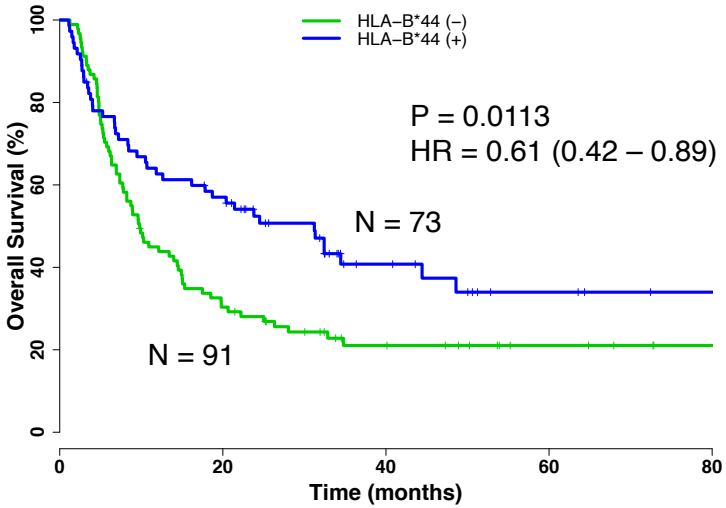

Allele	Freq (%)	HR	P-value
B1801	7.9	0.436	0.05
B3701	3.05	0.93	0.90
B4001	6.1	1.08	0.83
B4002	4.88	1.13	0.80
B4101	1.22	0.564	0.60
B4402	14.02	0.688	0.22
B4403	9.15	0.566	0.12
B4405	1.83	0.31	0.25
B4501	0.006	1.21×10^{-7}	1.00
B5001	1.83	0.23	0.17

Discovery (Cohort 1)

Cohort 1: Patients with melanoma treated with anti-CTLA-4 (N = 164) or anti-PD-1 (N = 105)

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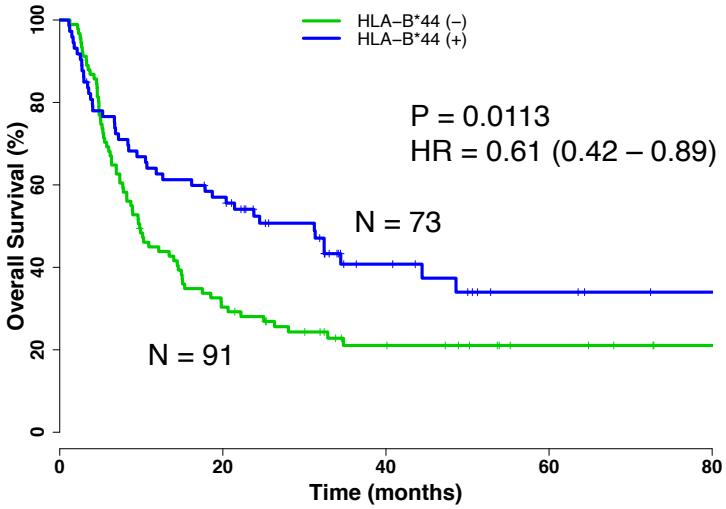
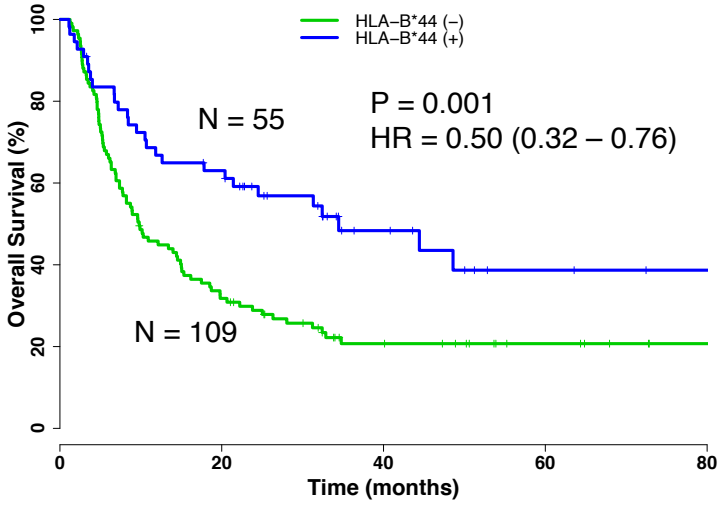
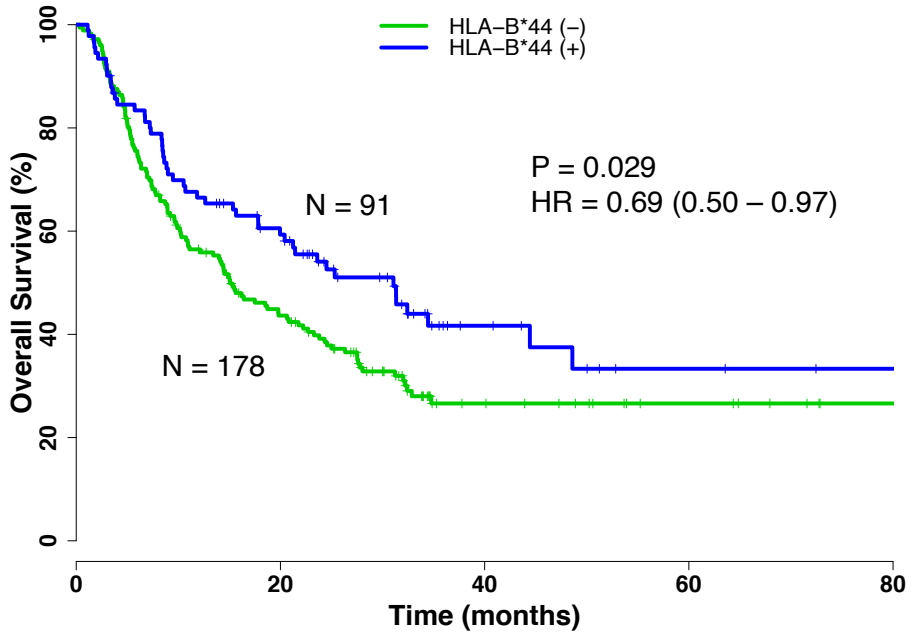




HLA-B*18:01, HLAB*44:02, HLA-B*44:03, HLA-B*44:05, and HLAB*50:01

Cohort 1: Patients with melanoma treated with either anti-CTLA-4 (N = 164) or anti-PD-1 (N = 105)



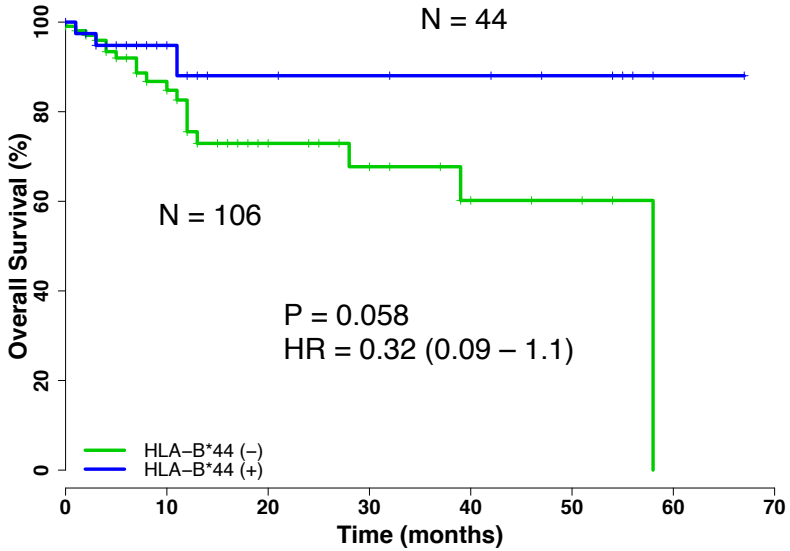
HLA-B*18:01, HLAB*44:02, HLA-B*44:03, HLA-B*44:05, and HLAB*50:01

Validation (Cohort 2)

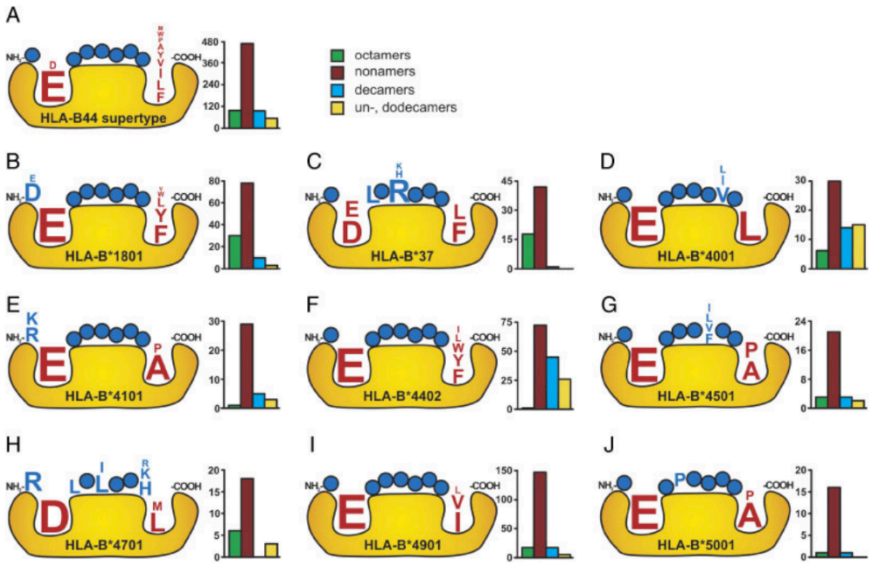
Cohort 2: Patients with melanoma treated with either anti-CTLA-4 (N = 36) or anti-PD-1 (N = 114)

3 Perform survival analysis in cohort 2 of patients with presence of previously identified B44 alleles from cohort 1 and patients without these B44 supertype alleles

HLA-B*18:01, HLAB*44:02, HLA-B*44:03, HLA-B*44:05, and HLAB*50:01

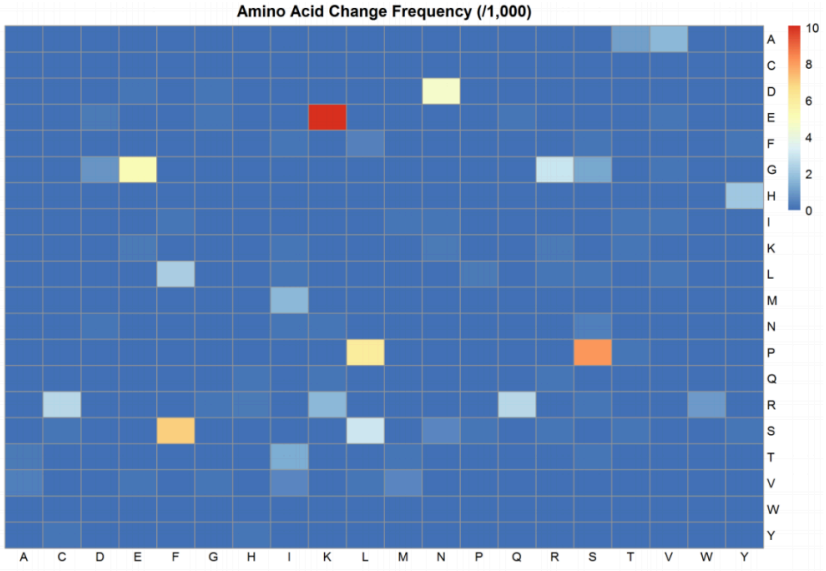


Peptide motifs profiles of the HLA-B44 supertype alleles



Amino acid mutation signatures in melanoma

Glycine (G) > Glutamic acid (E)



From

To

Summary

- Patient genotype diversity (at both the germline and somatic level) as well as tumor genetic diversity are critical contributors to the immune landscape and response to checkpoint blockade immunotherapy

- Prospective analyses are necessary to further validate these findings

- Further studies of large patient cohorts are required to identify other specific HLA class I alleles associated with repose after ICB therapy

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Collaborators outside MSK

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• Jedd Wolchok
•Matt Hellmann
• Alex Snyder (Chan Lab grad)