T and B cell receptor sequences and their usage in tumor immunotherapy

Sacha Gnjatic, PhD

Associate Professor
Departments of Medicine, Oncological Sciences, Pathology
Tisch Cancer Institute and Precision Immunology Institute
Icahn School of Medicine at Mount Sinai, New York NY
Co-Director of the Human Immune Monitoring Center

Precision
Immunology
Institute

The Tisch
Cancer
Institute

Disclosure information: Sacha Gnjatic, PhD

The following relationships exist:

Regeneron: Research Support
Janssen R&D: Research Support
Genentech: Research Support
Takeda: Research Support
BMS: Research Support
Boehringer Ingelheim: Research Support
Celgene: Research Support

Co-inventor on an issued patent for multiplex immunohistochemistry to characterize tumors and treatment responses (MICSSS). The technology is filed through Icahn School of Medicine at Mount Sinai (ISMMS). Mount Sinai has received payments associated with licensing this technology and both Mount Sinai and Dr. Gnjatic are entitled to future payments.

OncoMed: Past Consulting Fees (e.g., advisory boards)
Merck: Past Consulting Fees (e.g., advisory boards)

Cancer Immune Monitoring and Analysis Centers and Cancer Immunologic Data Commons

The CIMAC-CIDC Network: A Cancer Moonshot Initiative (U24)

The CIMAC-CIDC network will provide a standing infrastructure of bioassays and data commons for correlative studies in NCI-funded trials involving immunotherapy ($50M+)

- 4 CIMACs for scientific expertise and a wide range of highly specialized services using state-of-the-art equipment
- One CIDC for centralized bioinformatics resources for data collection and integration across trials and clinical databases

Scope of work

- Support correlative studies in early (phase 1 / 2) immunotherapy trials in the CTEP Trial Networks and Grant-supported trials
- 500 patients / multiple timepoints / year for comprehensive profiling
- Many additional patients from industry and non-NCI trials through Partnership for Accelerating Clinical Trials (PACT, $220M)

NIH NATIONAL CANCER INSTITUTE

CIMAC-CIDC Immuno-Oncology Biomarkers Network

FNIH Foundation for the National Institutes of Health

AbbVie, Amgen, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Novartis, Pfizer

CIMAC-CIDC Network

CIMAC-CIDC Immuno-Oncology Biomarkers Network

CANCER MOONSHOT

NIH NATIONAL CANCER INSTITUTE

Laboratory Coordinating Committee (LCC)

FNIH Foundation for the National Institutes of Health

Cancer Immune Monitoring and Analysis Centers (CIMACs)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Ignacio Wistuba
Cara Haymaker
Gheath Al-Atrash

Mount Sinai
Sacha Gnjatic

Dana-Farber Cancer Institute
Cathy Wu
Steve Hodi

Stanford MEDICINE
Holden Maecker
Sean Bendall

Each CIMAC will contribute to specific assays or trials across the networks

NCTN
- SWOG
- ECOG-ACRIN

NCTN
- NRG
- Alliance

ABTC

PACT
AbbVie
Amgen
Boehringer I
BMS
Celgene
Genentech
Gilead
GSK
Janssen
Novartis
Pfizer
Sanofi

ETCTN

CITN

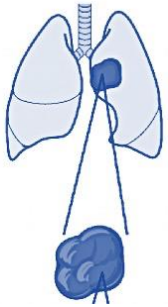
COG
Ped-CITN
PBTC

Cancer Immune Data Commons (CIDC)
Shirley Liu, Ethan Cerami

Dana-Farber Cancer Institute

Assays and platforms for monitoring https://cimac-network.org

Tier 1: recommended for all trials and chosen for balance between reproducibility/feasibility and innovation



Tier 1	Tier 1 alternate if sample issues/allows	Tier 2	Tier 3
WES	Targeted mutation panel		
RNAseq	Nanostring (low RNA quality score)	scRNAseq	CITEseq
mIHC/IF		MIBI, ISH	HTG GeoMx, Visium 10x
PD-L1 IHC			
TCRvß Adaptive	TCR from RNA, alpha/beta paired chains	**TCRvß** Adaptive	scTCRseq
CYTOF (pheno)	Flow cytometry	CYTOF (functional)	
		ELISPOT neoAg	ICS, Ag-specific cell sorting
			Tetramers
Olink PEA	Luminex multiplex		
ELISA TAA-Ab		ELISA TAA-Ab	Seromics (protein arrays)
ct/cfDNA		ct/cfDNA	CTC, exosomes
		ATACseq	RRBS, scATACseq
16S Microbiome		16S Microbiome	Shotgun metagenomics

Scope – Background, Methodologies, Applications

Applications:

- Analyze repertoire properties as potential biomarker:
  number of different clones, T cell repertoire diversity, clonality/entropy
- Analyze repertoire dynamics as potential biomarker:
  clonal expansion, changes with treatment
- Tracking T or B cell specificity at the gene level over treatment using receptor variable sequences as barcode
- Characterize TCR alpha-beta sequences for adoptive transfer
- Characterize BCR sequences for heavy-light chains for mAb or CAR-T
- Minimal residual disease (BCR) tracking

Challenges:

- Using TCR information to predict antigen specificity
- Coverage / sensitivity / errors / PCR expansion bias
- Adapting tests to formalin-fixed tissues with degradation (DNA/RNA, short/long reads)
- “Public”, i.e., shared TCR sequences

TCR repertoire applications

Transplant International 2019; 32: 1111-1123

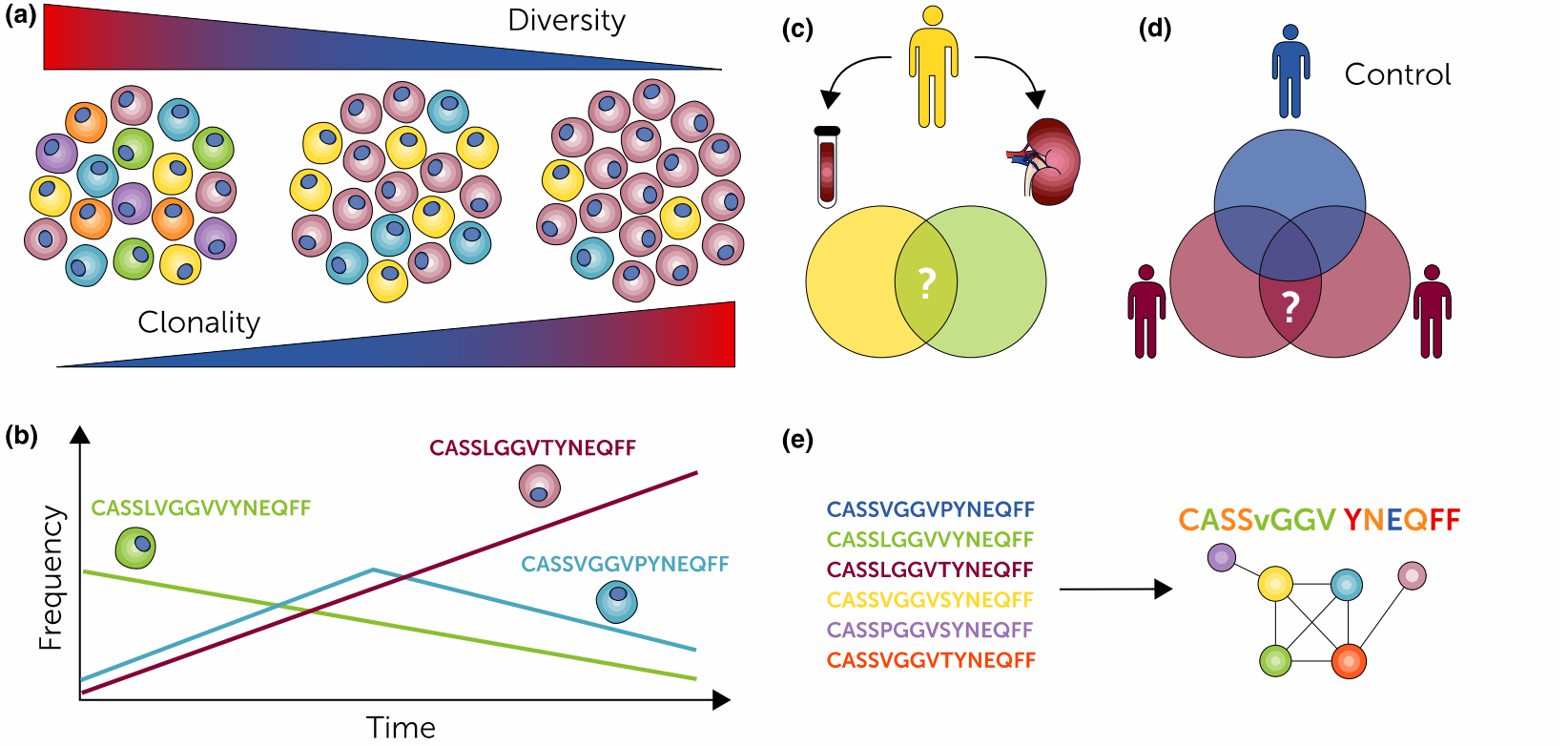
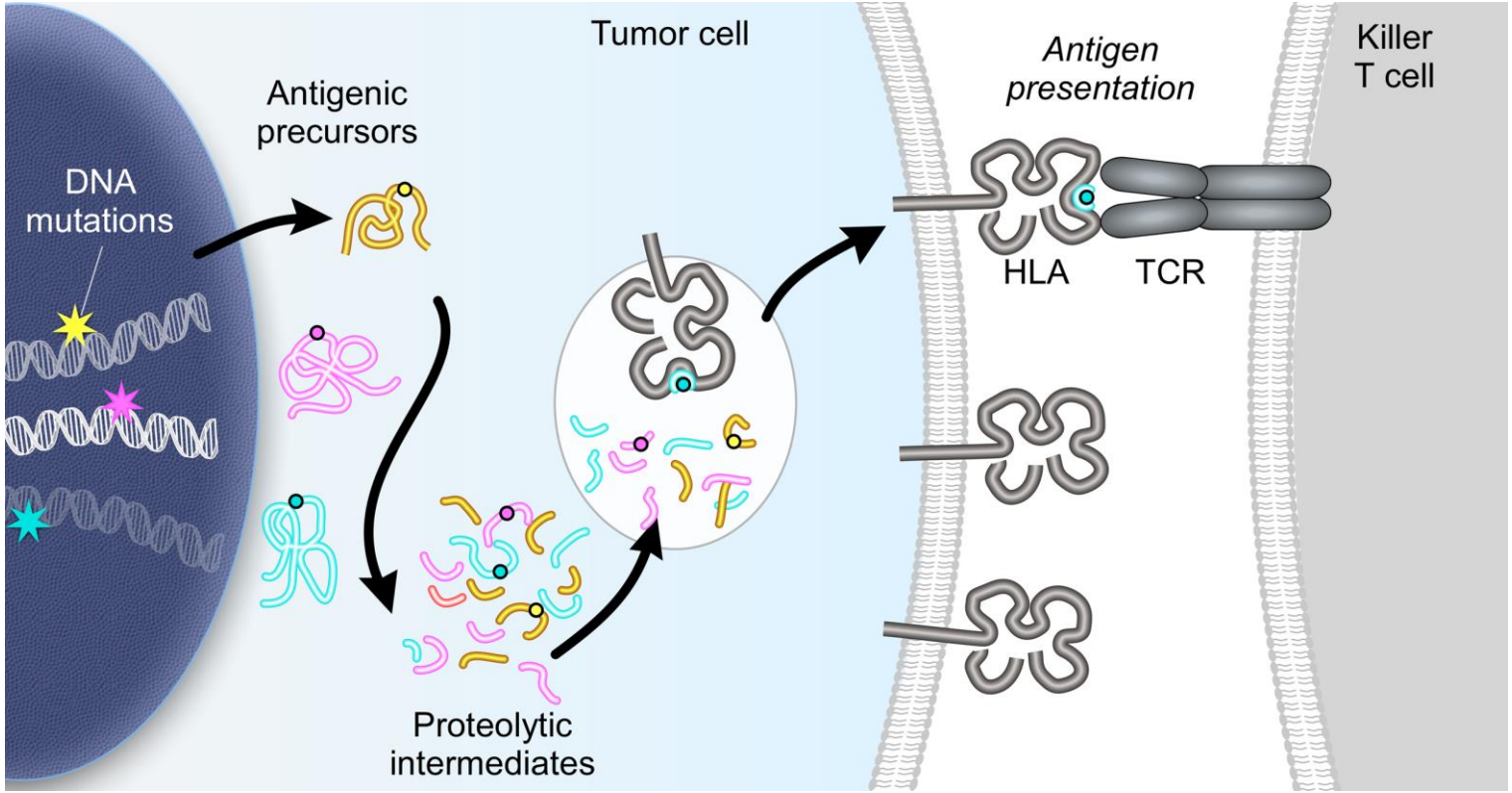


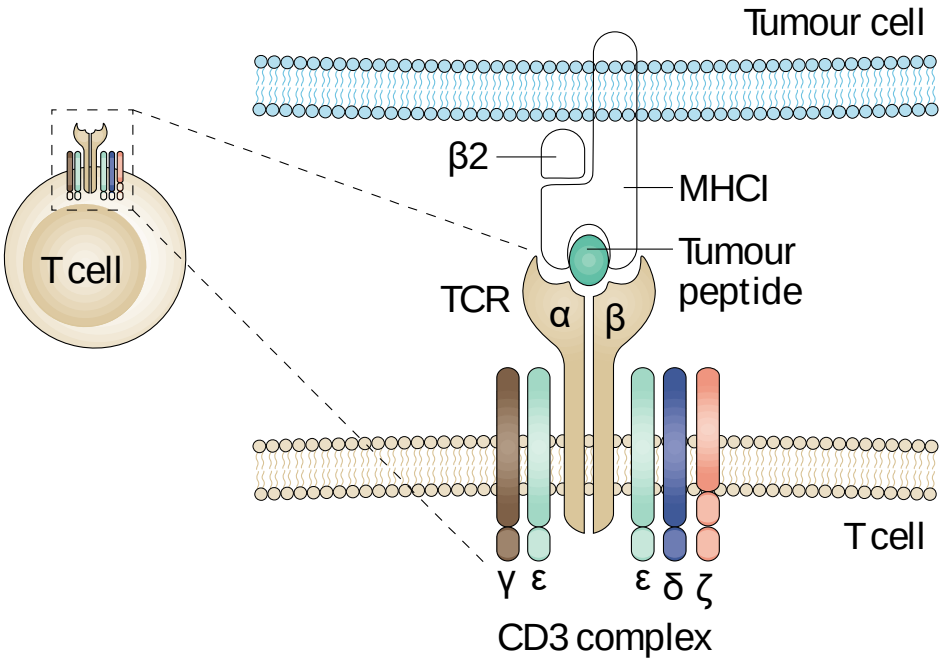
Figure 2 Insights from immune repertoire analysis. Analysis of repertoire data can offer a variety of valuable immunological information, including: (a) clone size distribution statistics such as diversity and clonality, (b) tracking of clones in time, (c) physical/phenotypic space, (d) sharing between individuals and (e) clonal sequence features (motifs, VJ-usage biases etc.).

Somatic mutations generate neoantigens

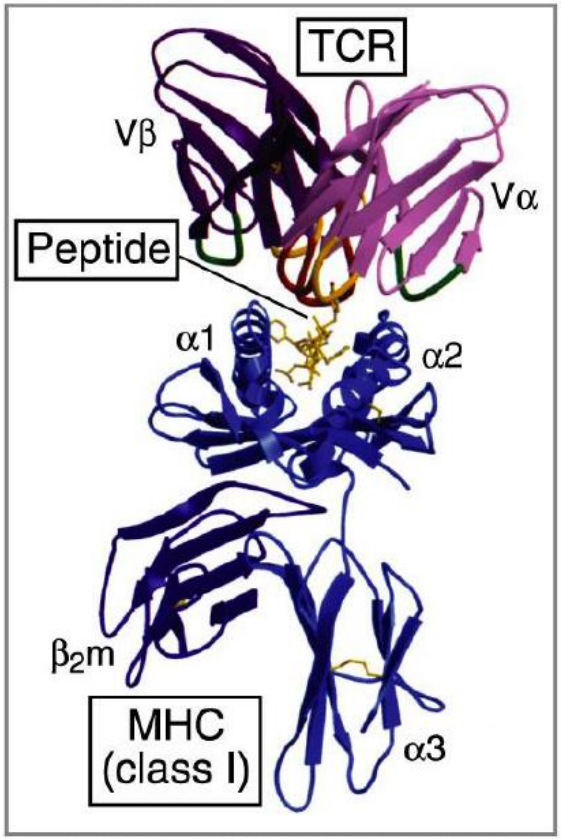


Cold Spring Harb Perspect Med. 2017;7:a026740.

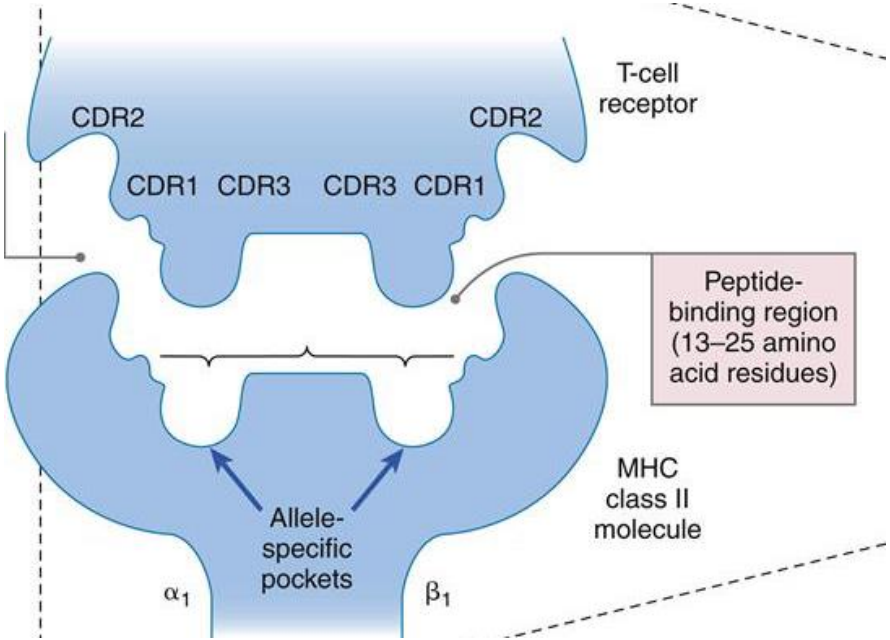
Peptide presentation

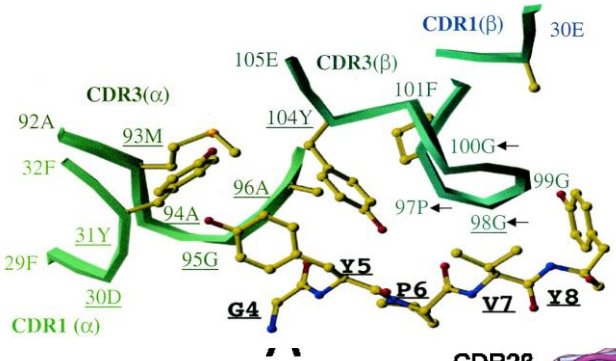


The recognition of a peptide-MHC complex by a T cell antigen receptor.

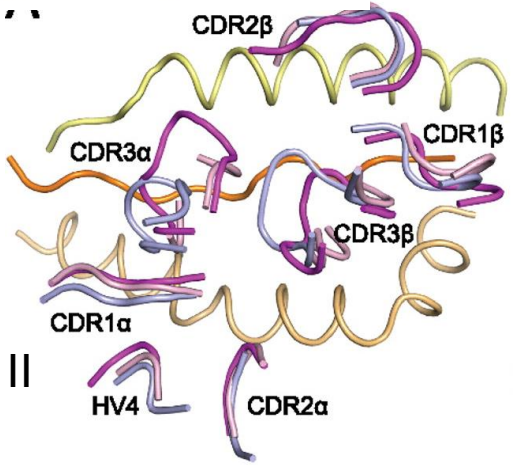


CDR3 region from TCR Vbeta as the biggest contributor to antigen specificity





HLA class I



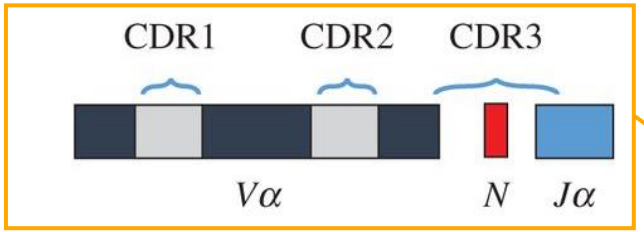
HLA class II

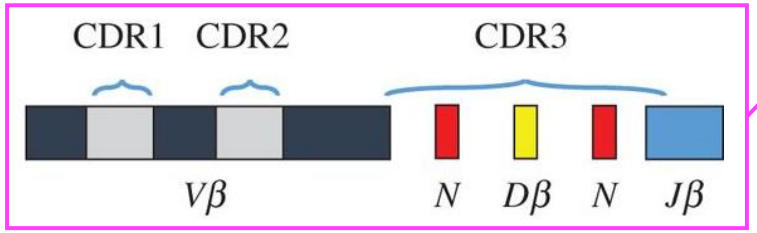
https://clinicalgate.com/surface-interactions-between-t-cells-and-antigen-presenting-cells/

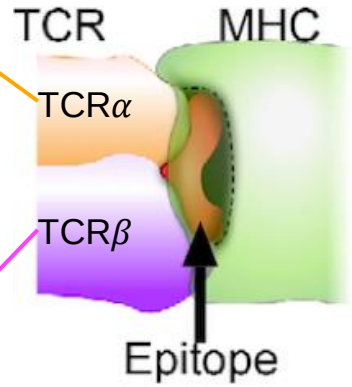
Journal of Virology 2001, 75:9836-9843

J Immunol, 2011, 186:5823-5832

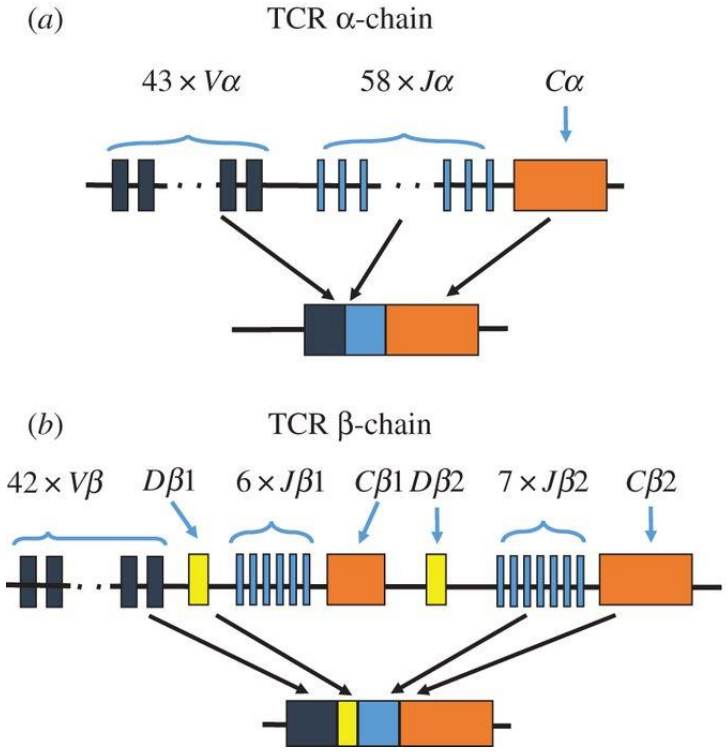
T cell receptor diversity





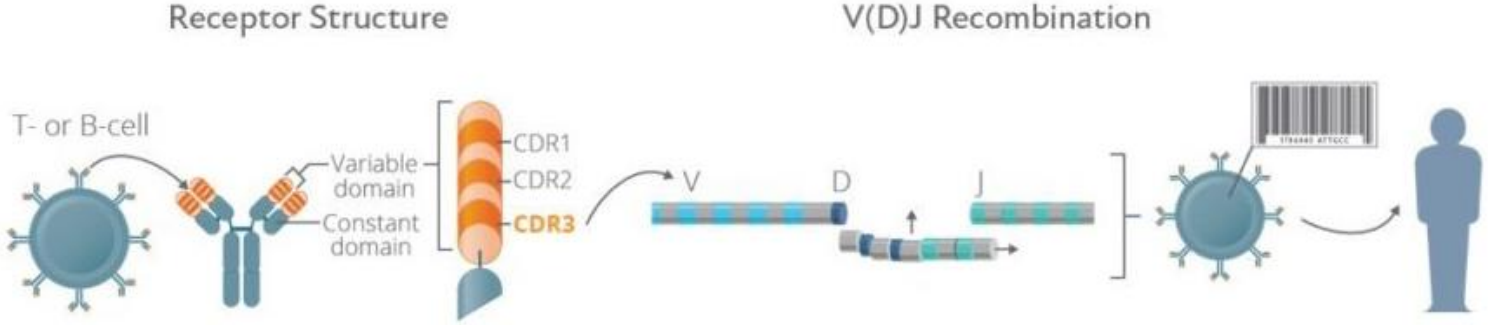


	V	D	J
TCRα	46	0	49
TCRβ	56	2	13



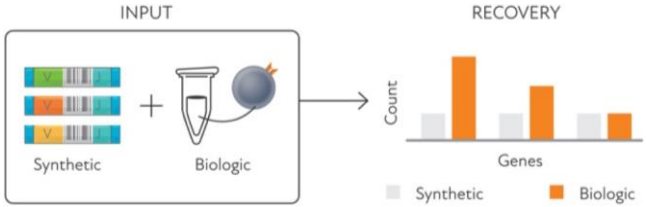
Philos Trans R Soc Lond B Biol Sci. 2015; 370: 20140291

Adaptive Biotech Immunoseq TCR Beta Sequencing

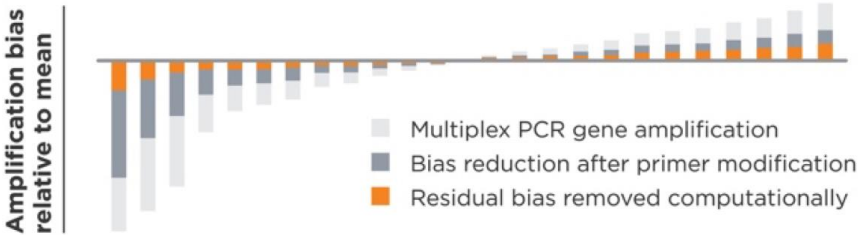


Synthetic repertoire for all VDJ gene combinations

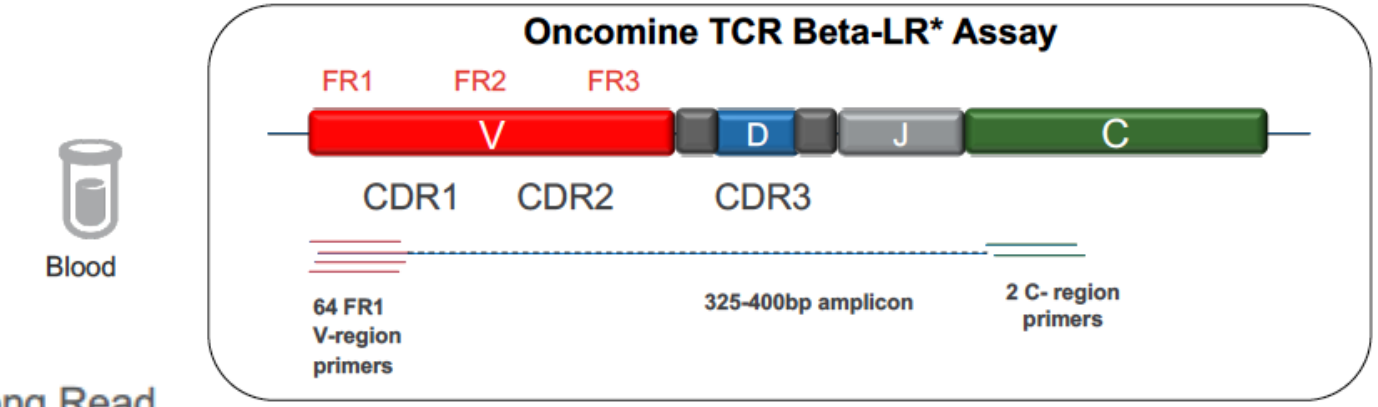
Additional controls per sample with more adjustments and absolute counts of immune cells



Adjust primer concentration to reduce amplification bias



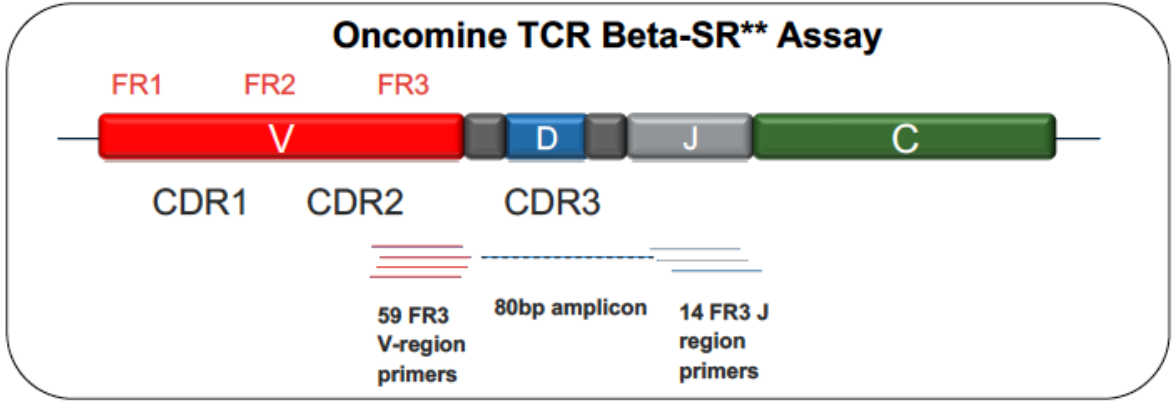
Oncomine TCR Beta Sequencing



Blood

*LR = Long Read
**SR = Short Read

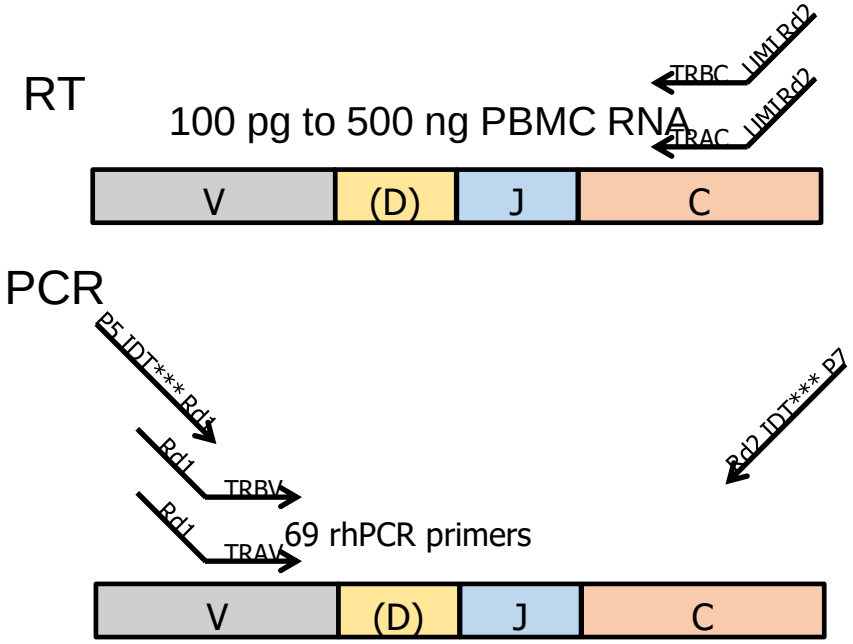
Ion-Torrent based



Blood/FFPE

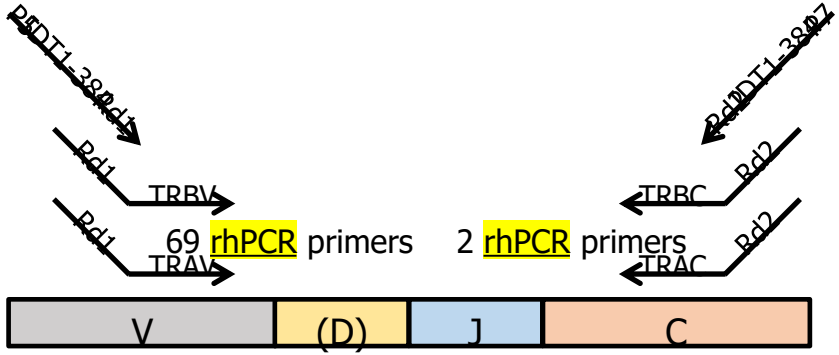
RNA-based sequencing (Ken Livak, DFCI)

rhTCRseq on bulk RNA



Pool samples & perform P5/P7 PCR

rhTCRseq re-amplifies TCR segments from cDNA



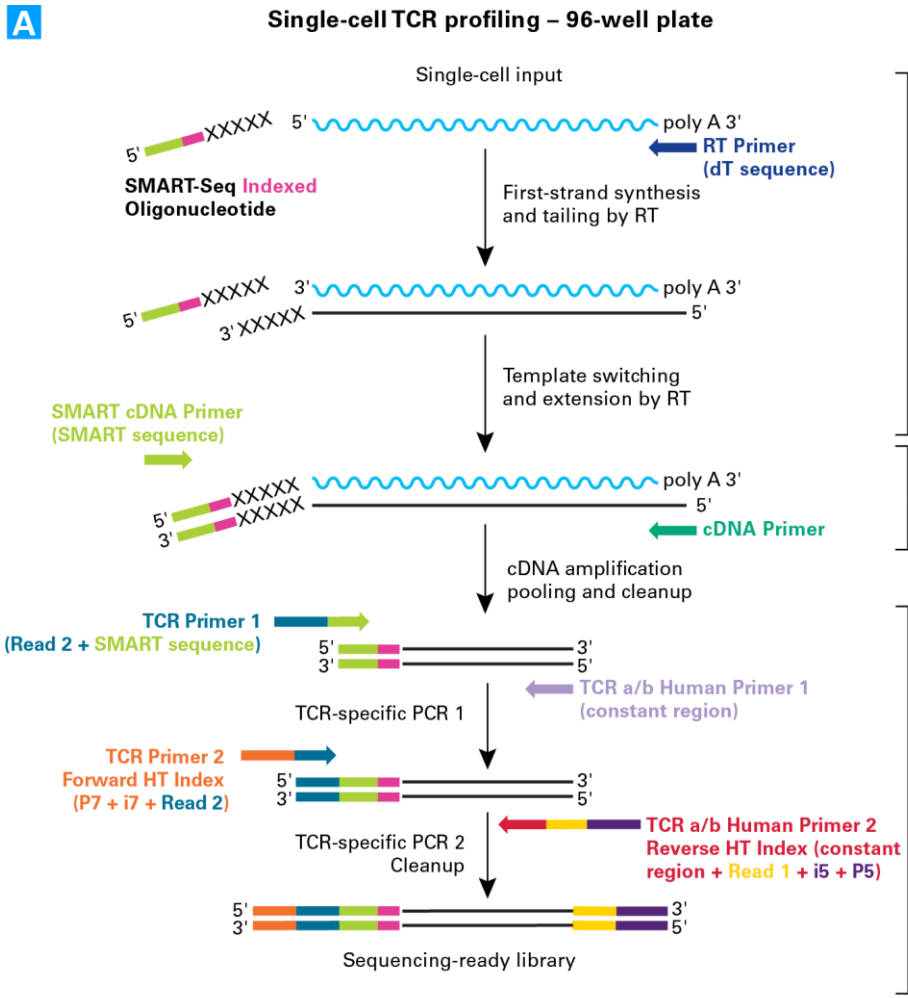
Pool samples & perform P5/P7 PCR

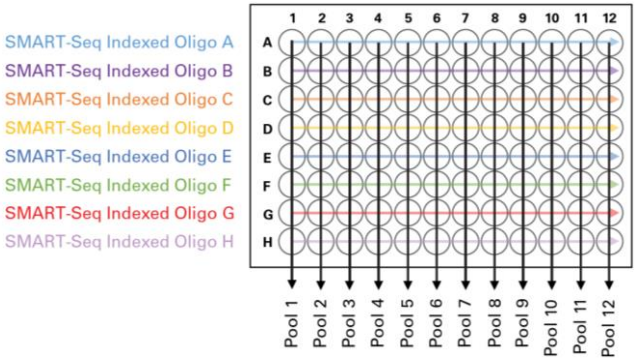
Start with full-length cDNA library
from template-switch procedure like Smart-seq2

Ken Livak. *Nat Protoc*. 2019 14:2571-2594

Single Cell Sequencing

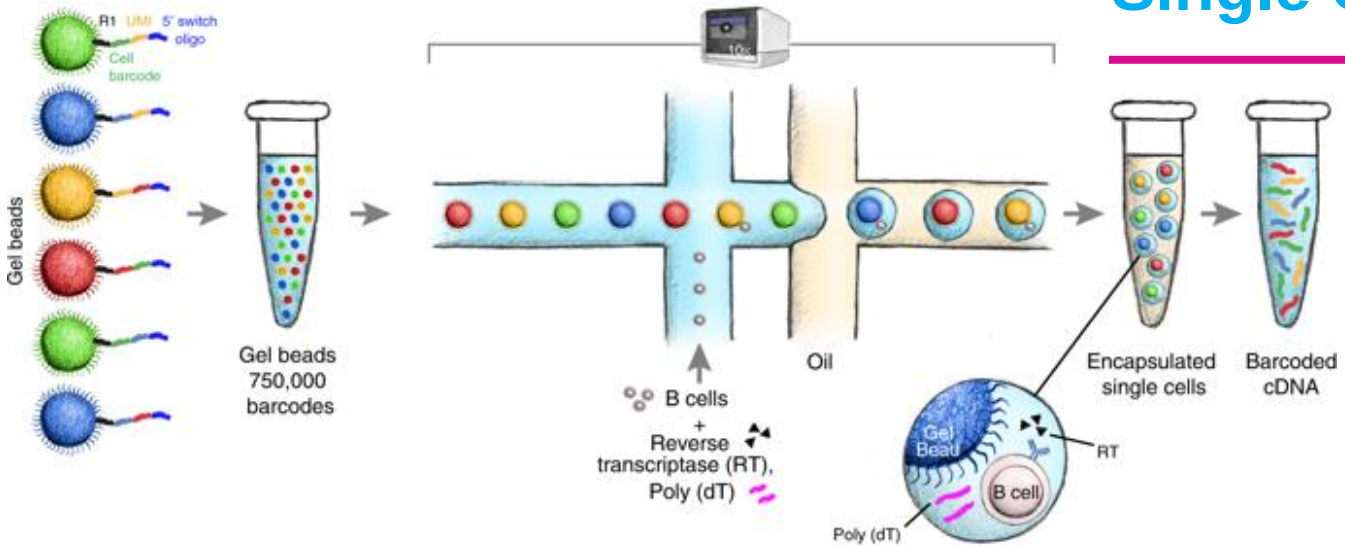
scTCRseq – 96 well plate

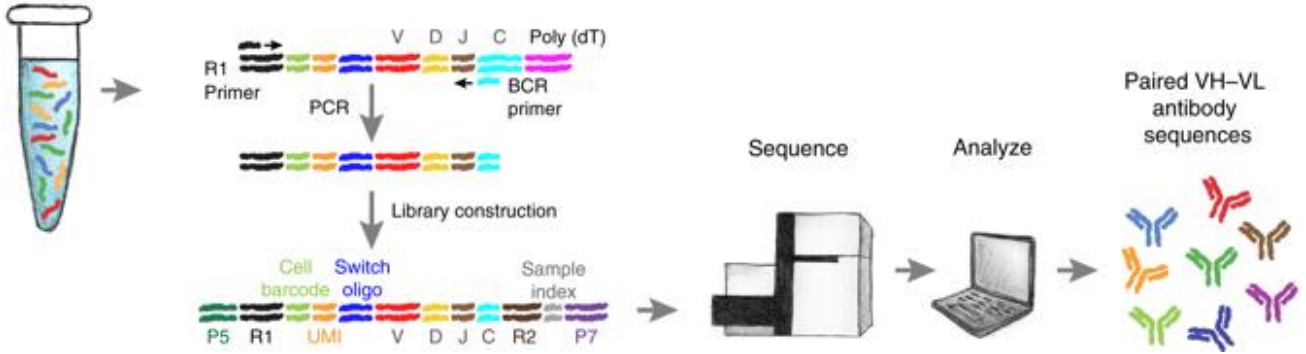




https://www.takarabio.com/products/next-generation-sequencing/immune-profiling/human-sctcr-profiling-kit-for-illumina-sequencing

Single Cell Sequencing



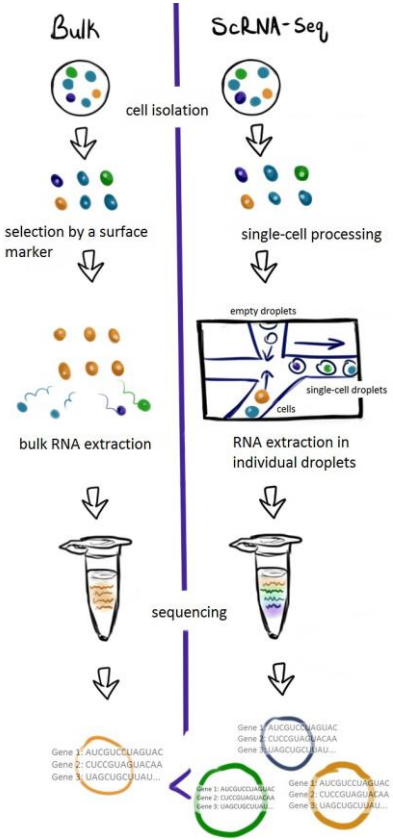


scTCRseq – 10X Genomics 5' kit

Communications Biology 2019; 2:304

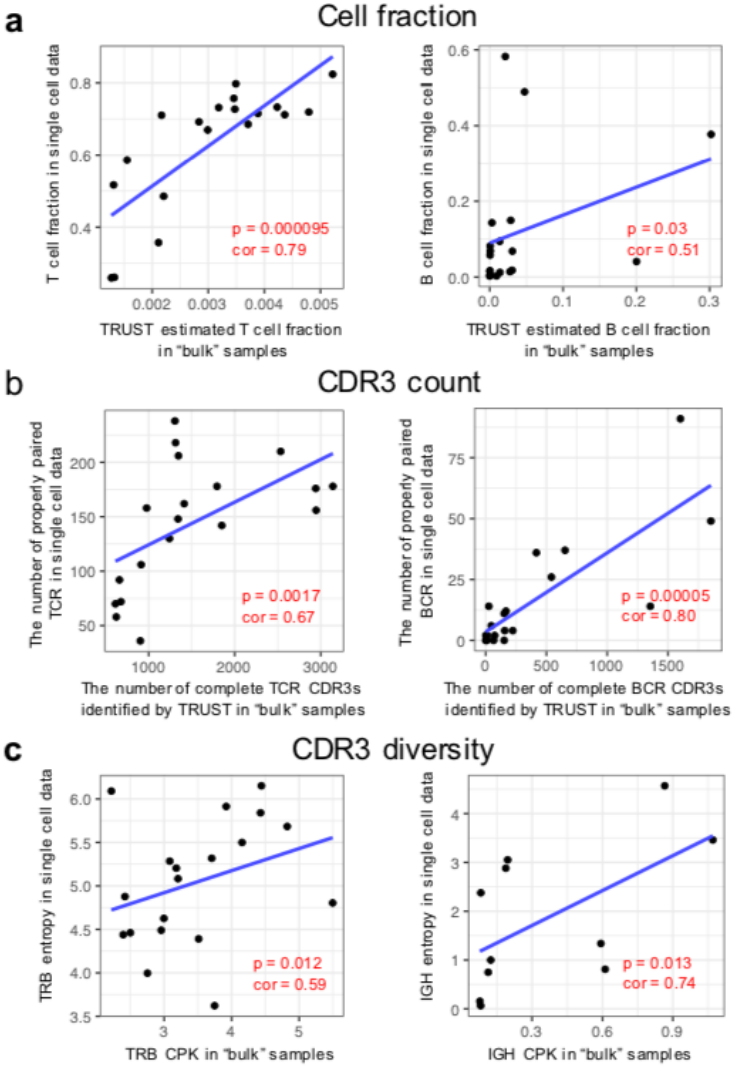
Inferring TCR and BCR information from bulk seq data

Several algorithms exist, including TRUST, validated here with scRNAseq data



http://sitn.hms.harvard.edu/flash/2017/single-cell-revolution-zooming-human-health-disease/

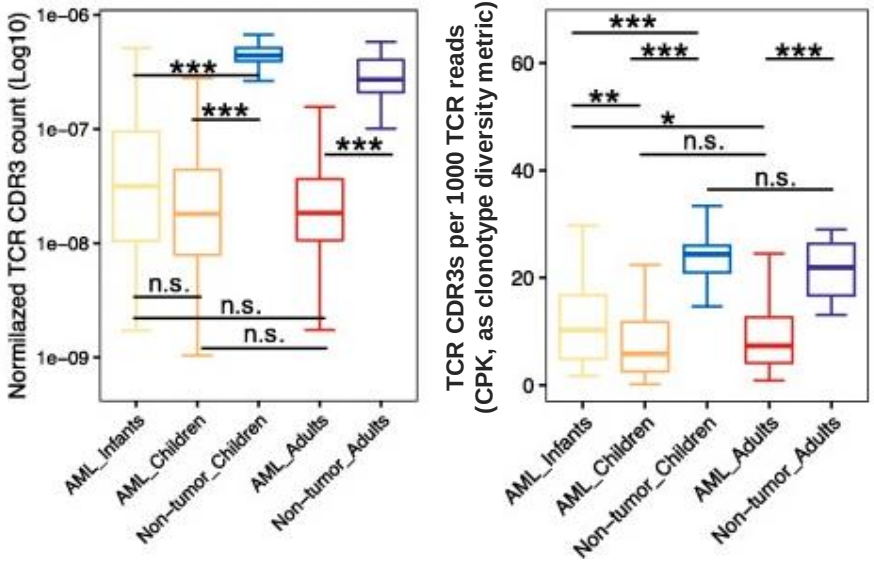
Genome Med. 2019 Nov 26;11(1):73



Immune receptor repertoires in pediatric and adult acute myeloid leukemia

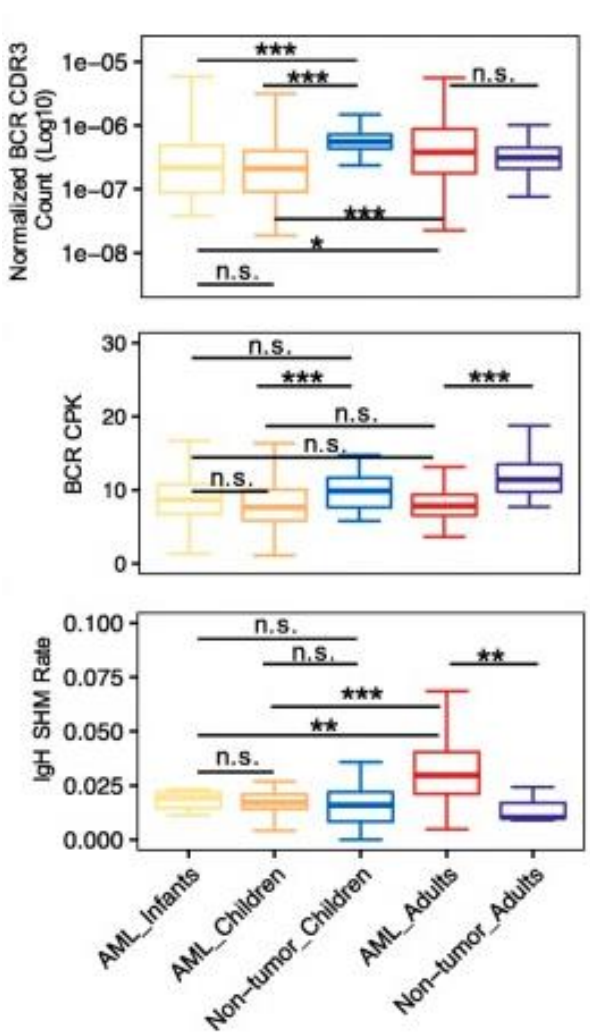
Higher clonal expansion of both T cells and B cells in the AML microenvironment.

T cells



By inference from RNAseq using TRUST algorithm

B cells



Genome Med 11, 73 (2019)

Convergence as new proposed metric

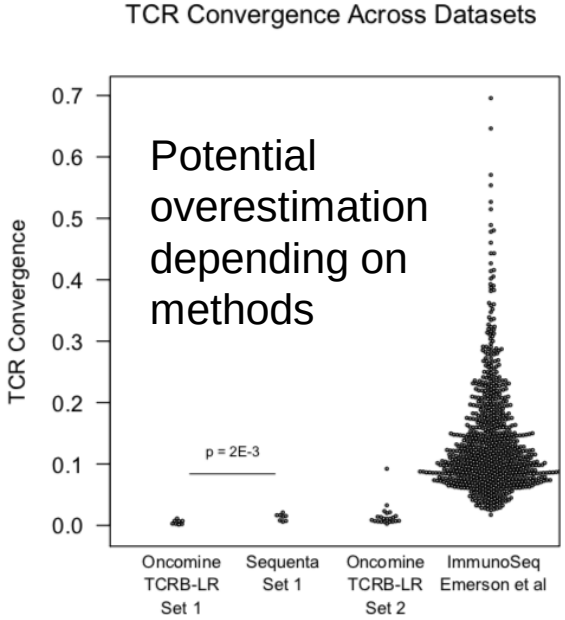
- Convergent TCRs are identical in amino acid space but different in nucleotide space
- Instances where T cells independently underwent VDJ recombination and proliferated in response to a common antigen
- Proposed to serve as an indicator of the immunogenicity of tumor

	Survey	Deep
Oncomine TCRB-LR	30	31
ImmunoSeq TCRB	55	84

Survey: 2 PCR replicates sequenced to ~1M reads depth
Deep: 6 PCR replicates sequenced to ~1M reads depth

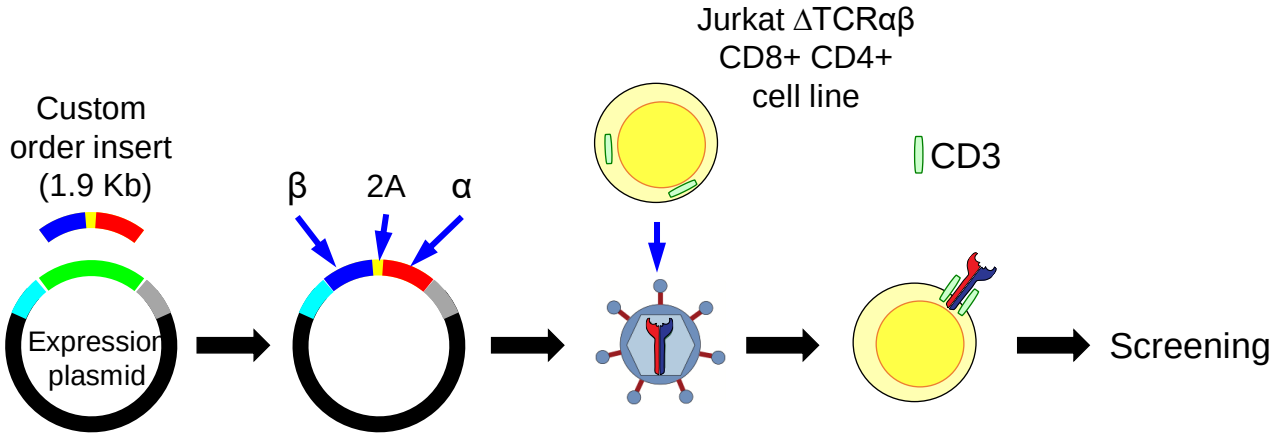
Input: 30 defined TCR plasmids

Possible unresolved sequencing or PCR derived artifacts



Front Immunol. 2020;10:2985

Cloning and expressing TCR



Useful for characterizing or confirming T cell specificity and for generating TCR-transduced cells for adoptive transfer

Applications

Higher intra-tumoral TCR clonality has been observed in responders to anti-PD-1 antibody treatment at both pre-treatment and during-treatment timepoints, whereas no such effect was observed for CTLA-4 blockade therapy [64–67].

In contrast, higher TCR repertoire diversity in the peripheral blood after CTLA-4 blockade was correlated with drug-related toxicities in prostate cancer [68,69] and metastatic melanoma [70].

It was recently shown that both PD1+CD8+ [79] and CD4+ Treg clonotypes [80] from peripheral blood match corresponding tumor-resident clones and appear to be tumor-reactive.

64. Amaria RN, Reddy SM, Tawbi HA, et al. Publisher correction: neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. Nat Med 2018; 24: 1942.

65. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018; 378: 1976.

66. Roh W, Chen PL, Reuben A, et al. Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. Sci Transl Med 2017; 9: eaah3560.

67. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014; 515: 568.

68. Oh DY, Cham J, Zhang L, et al. Immune toxicities elicted by CTLA-4

blockade in cancer patients are associated with early diversification of the T-cell repertoire. Cancer Res 2017; 77: 1322.

69. Subudhi SK, Aparicio A, Gao J, et al. Clonal expansion of CD8 T cells in the systemic circulation precedes development of ipilimumab-induced toxicities. Proc Natl Acad Sci USA 2016; 113: 11919.

70. Robert L, Tsoi J, Wang X, et al. CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res 2014; 20: 2424.

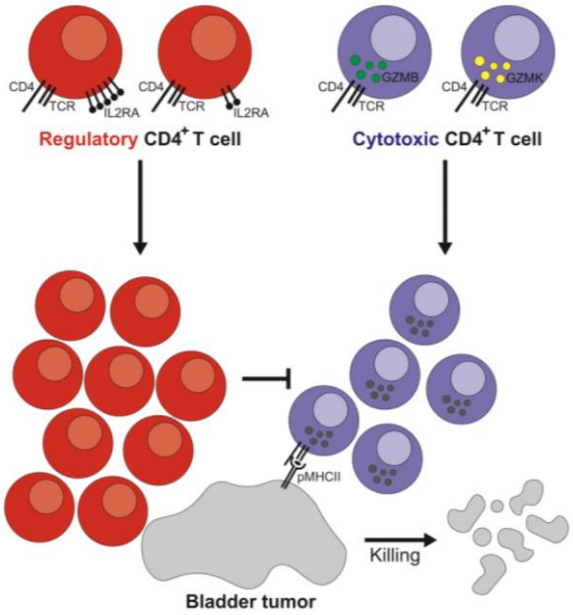
79. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med 2016; 22: 433.

80. Ahmadzadeh M, Pasetto A, Jia L, et al. Tumor-infiltrating human CD4(+) regulatory T cells display a distinct TCR repertoire and exhibit tumor and neoantigen reactivity. Sci Immunol 2019; 4: eaao4310.

Clonally expanded intratumoral cytotoxic CD4 T cells in bladder cancer

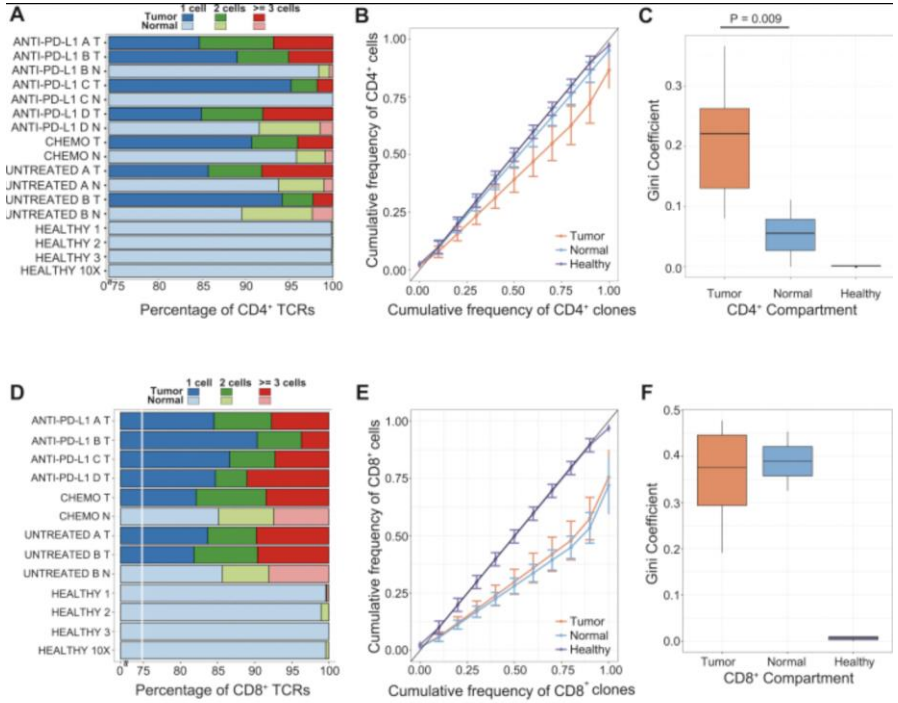
Larry Fong

Single-cell RNA and paired T cell receptor (TCR) sequencing of 30,604 T cells from 7 patients. We find that the states and repertoires of CD8+ T cells are not distinct in tumors compared with non-malignant tissues. In contrast, single-cell analysis of CD4+ T cells demonstrates several tumor-specific states, including multiple distinct states of regulatory T cells. Surprisingly, we also find multiple cytotoxic CD4+ T cell states that are clonally expanded. These CD4+ T cells can kill autologous tumors in an MHC class II-dependent fashion and are suppressed by regulatory T cells.



CD4

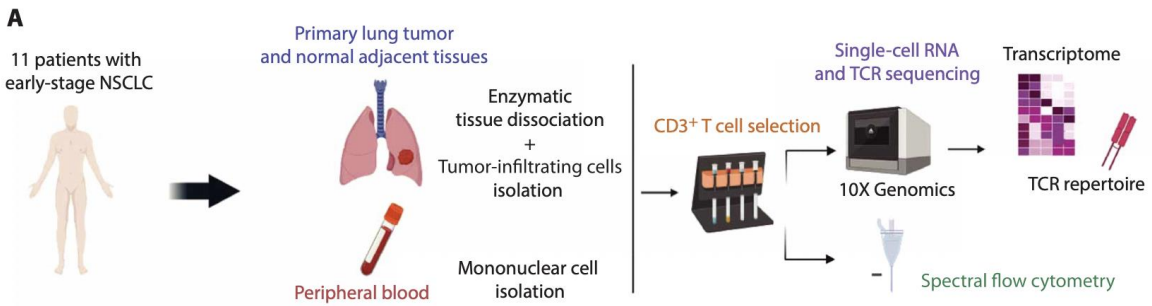
CD8

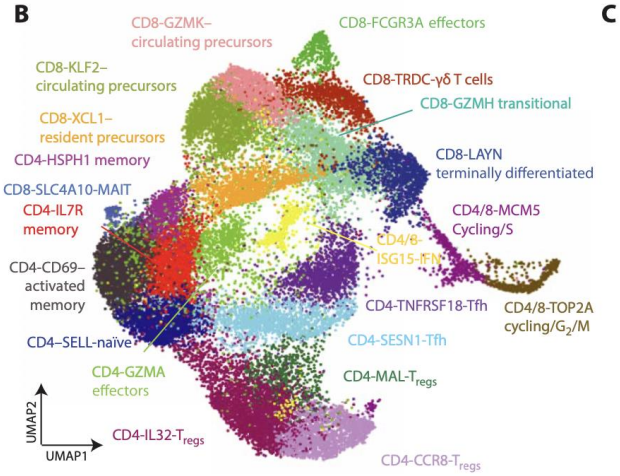


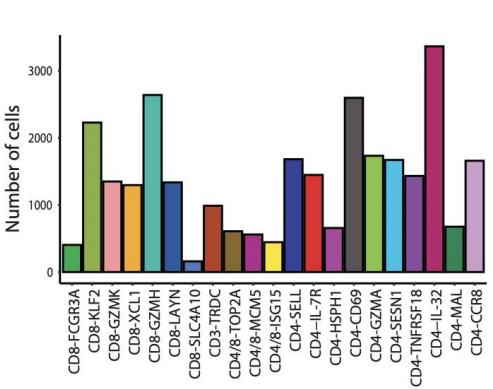
Cell. 2020 Jun 25;181(7):1612-1625.e13

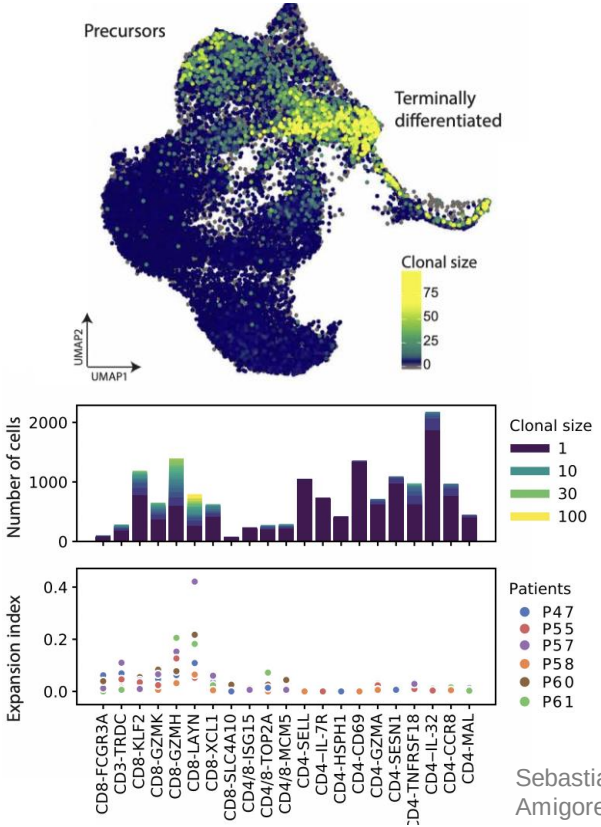
Tracking clonally expanded T cells and their transitional states in early NSCLC

Two precursor populations converge through a unique transitional state into terminally differentiated dysfunctional or exhausted cells, along with TCR expansion, and transition from precursor to late-differentiated states correlates with intratumor T cell cycling.







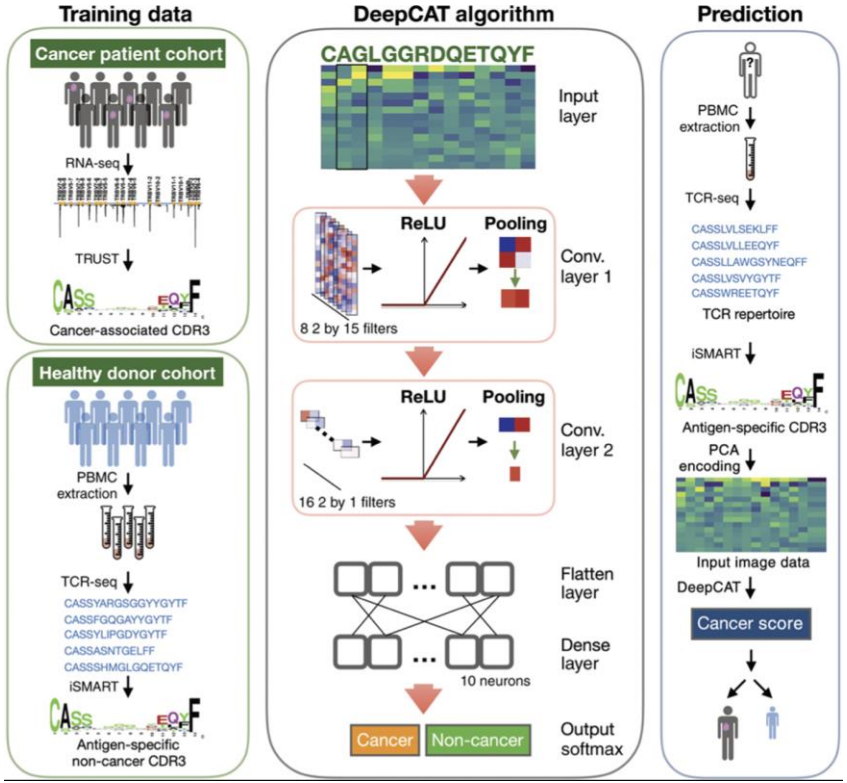


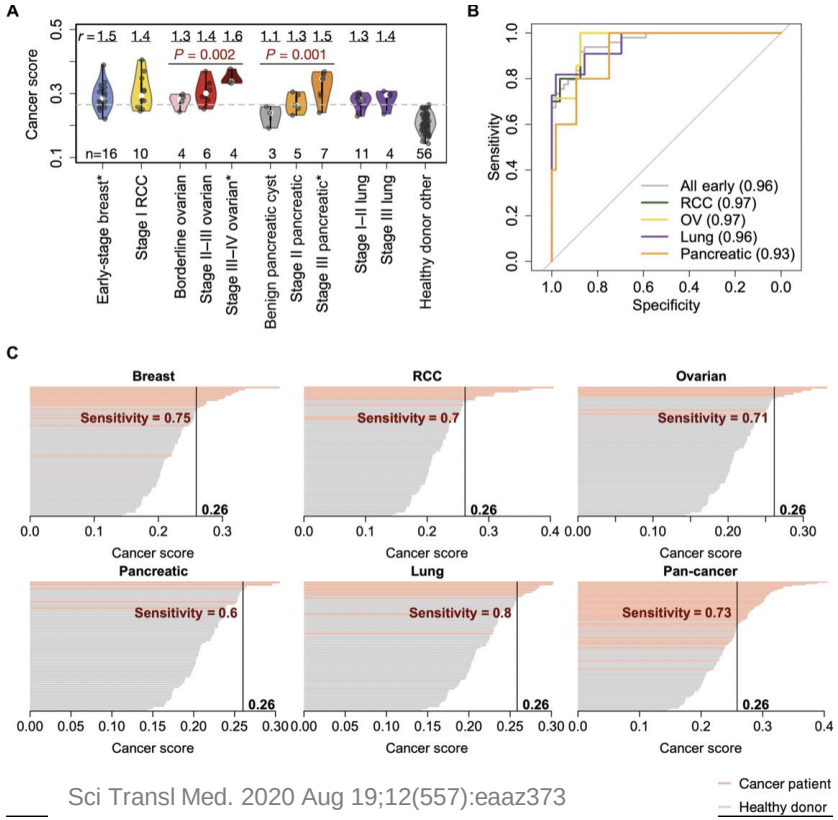
Sci Immunol. 2021 Jan 29;6(55):eabd577

Sebastian Amigorena

DeepCAT: a deep learning tool for de novo prediction of cancer-associated TCRs

Blindly apply DeepCAT to distinguish over 250 patients with cancer from over 600 healthy individuals using blood TCR sequences: high prediction accuracy (AUC ≥ 0.95) for multiple early-stage cancers for using peripheral blood TCR repertoire as noninvasive cancer detection.





Sci Transl Med. 2020 Aug 19;12(557):eaaz373

Serial biopsies in 25 melanoma patients

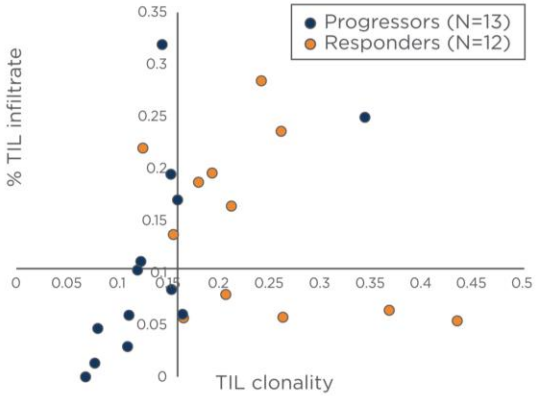
1. Biopsy → gDNA → **immunoSEQ® (TCRB)**
2. **Anti-PD-1 therapy**
3. Biopsy → gDNA → **immunoSEQ (TCRB)**

Comparing T cell repertoire clonality and abundance with anti-PD-1 therapy in advanced melanoma

Tumeh PC, et al. (2014) Nature 515(7528):568–71 (Adaptive Biotech.com)

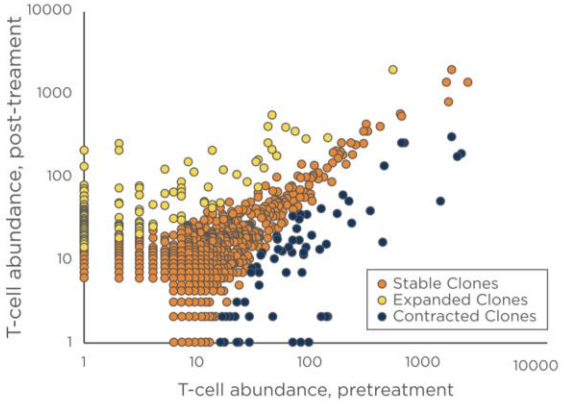
RESULTS

Quantitative sequencing of T-cell receptor beta (TCRB) in patients with melanoma

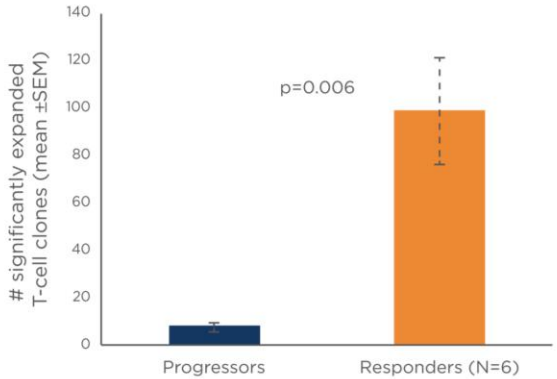


Progressors were associated with lower levels of TILs and lower TIL clonality

Measurement of drug effect in the tumor



Representative scatterplot of clones from a responding tumor



Clonal expansion in terms of clinical response

29 patients with urothelial carcinoma in a single arm, phase II clinical trial were evaluated.

1 Pre-treatment tumor → whole exome sequencing, RNA-seq and **immunoSEQ hsTCRB Assay**

2 Pre-treatment and serially collected post-treatment blood → **immunoSEQ hsTCRB A**

RESULTS

- Increased pre-treatment TIL density corresponded to DCB, but not continuous progression free survival (PFS).
- High diversity in pre-treatment blood is associated with improved PFS and overall survival (OS).
- Expansion of TIL clones (at 3 weeks after initiation of treatment) was pronounced in the post-treatment blood of patients with DCB.
- All patients with high diversity blood repertoires and increased TIL clonality survived over 1 year following treatment.
- No significant association between mutation burden or predicted neoantigen load with DCB or OS.

Figure 1. Tumor

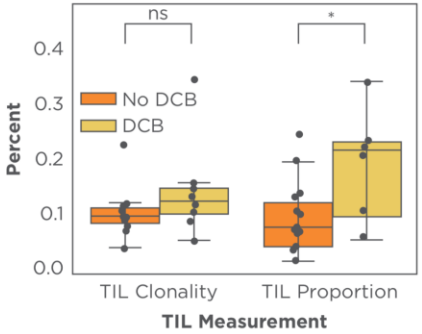
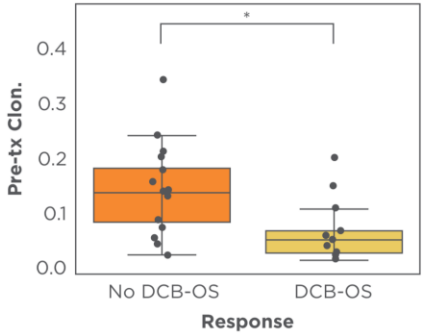


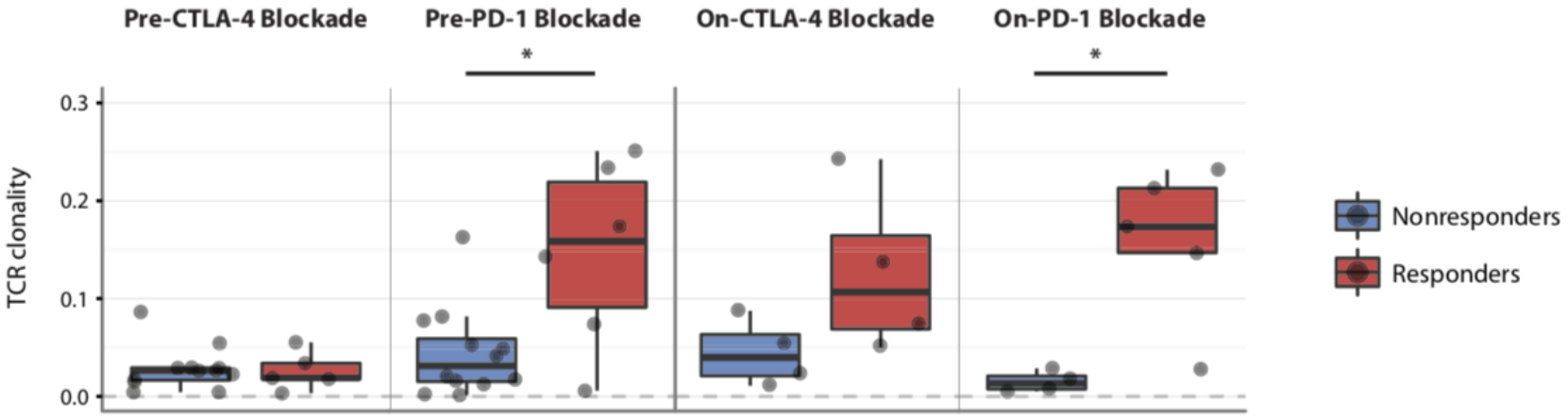
Figure 2. Blood



Contribution of systemic and somatic factors to clinical response and resistance to PD-L1 blockade in urothelial cancer: An exploratory multi-omic analysis

Snyder A, et al. PLOS Medicine. 2017; 14(5): e1002309.

Immune checkpoint blockade in melanoma leads to more clonal and diverse T cell infiltrate in responders



a more clonal T cell repertoire was predictive of response to PD-1 but not CTLA-4 blockade, already from baseline

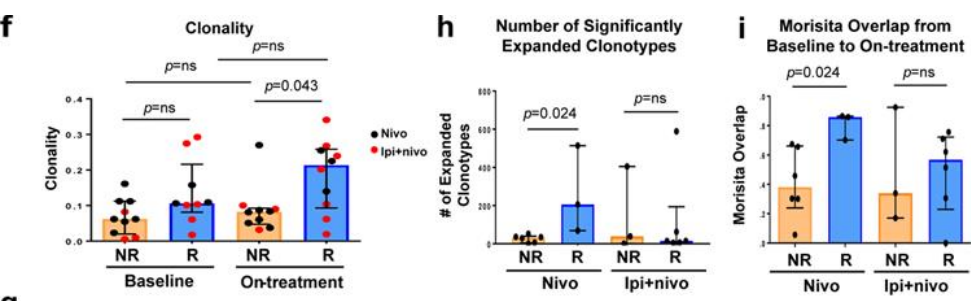
Roh et al., Sci. Transl. Med. 9, eaah3560 (2017)

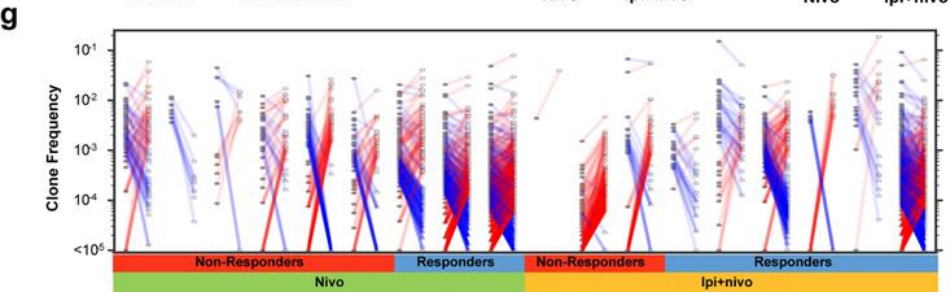
Clonality was measured as 1-(entropy)/log2(# of productive unique sequences), with entropy taking into account clone frequency

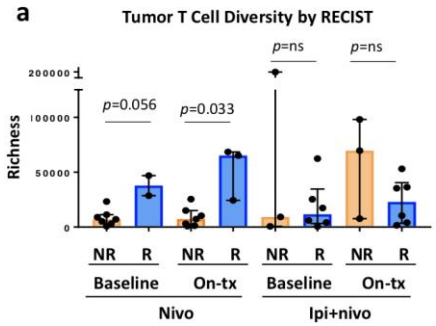
Neoadjuvant immune checkpoint blockade in melanoma (nivo or nivo+ipi) leads to more clonal and diverse T cell infiltrate (along with higher lymphoid infiltrate) in responders, but not in blood

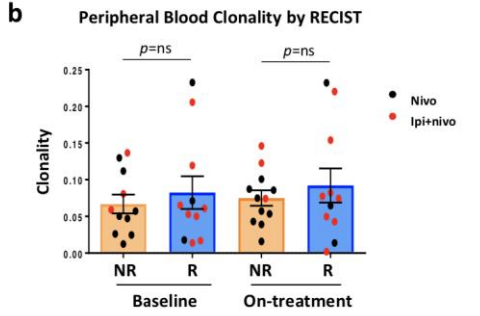
Tumor

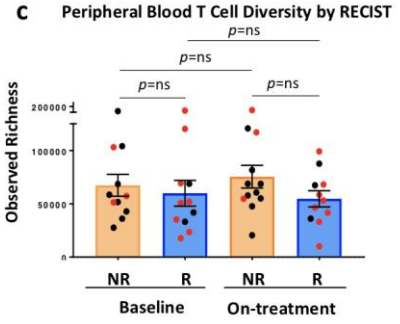
Blood

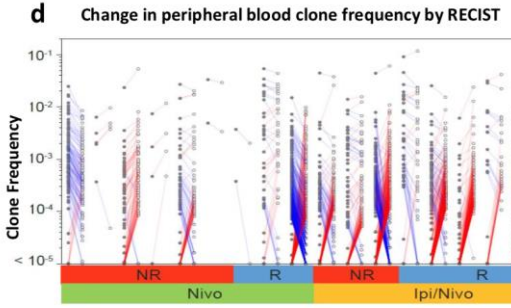






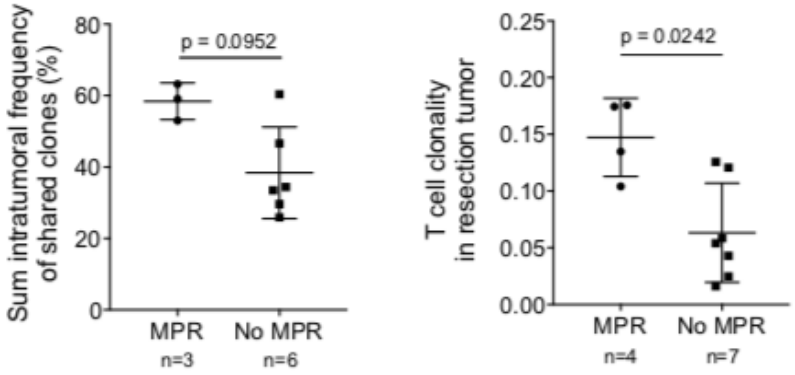




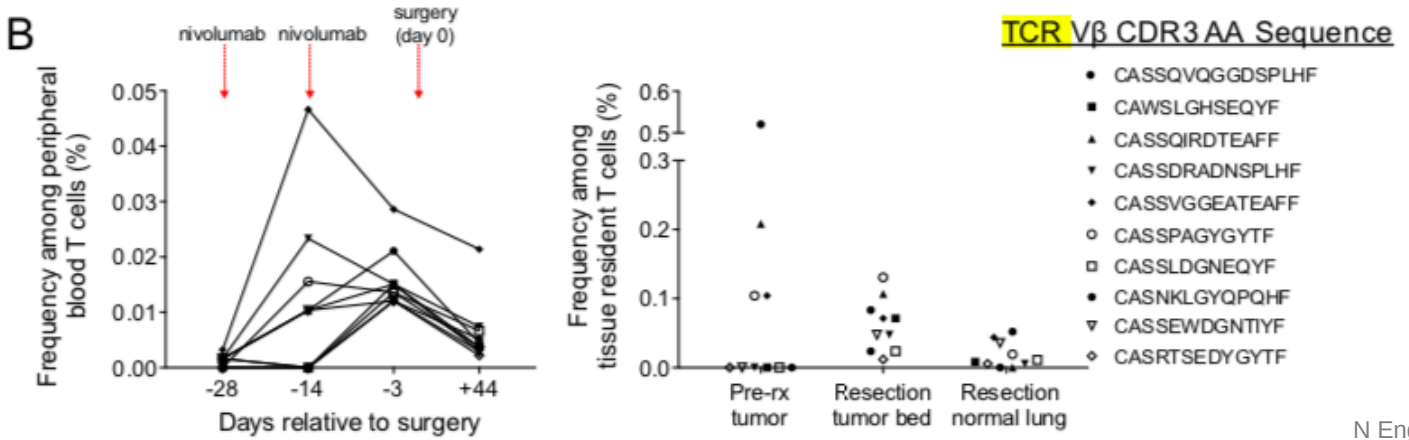


Nat Med. 2018;24:1941

Clonotypes through neoadjuvant PD-1 blockade in resectable lung cancer



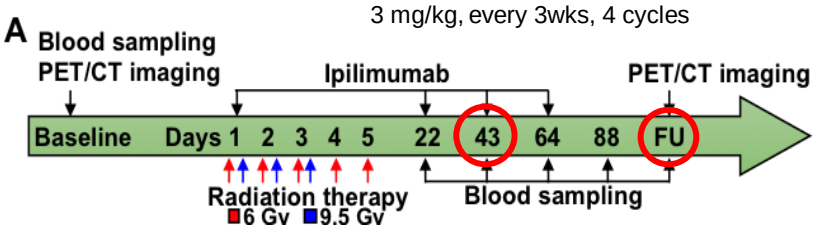
At the time of resection, tumors with a major pathological response had a higher frequency of T-cell clones that were shared between intratumoral and peripheral compartments and a higher clonality of the T-cell population (i.e., a higher proportion of total T cells constituted by a restricted number of distinct clones) than did tumors without a major pathological response



N Engl J Med 2018;378:1976-86.

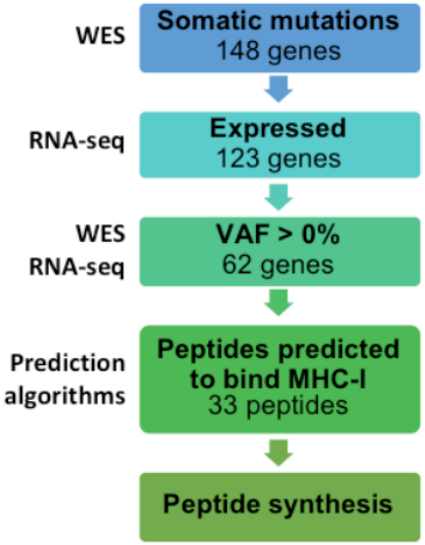
Example of NSCLC study combining radiotherapy and ipilimumab

Collaboration with C.Lhuillier and S. Demaria

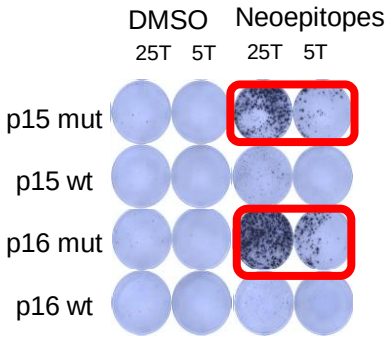


RT: to one metastasis, palliative dose (6 Gy x 5 or 9.5 Gy x 3)

Pt #4 with Complete Response

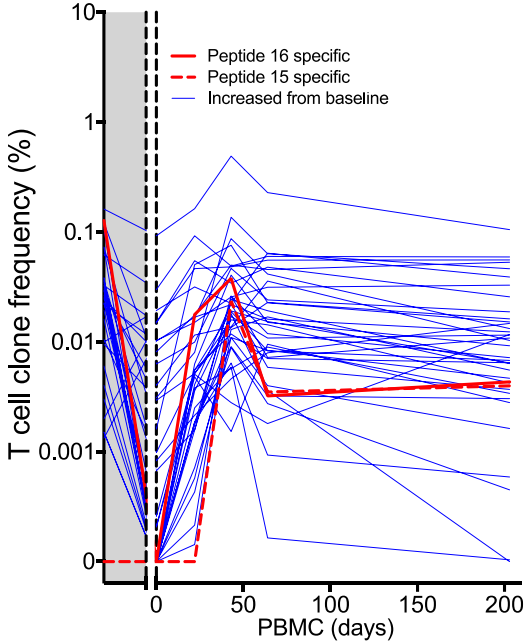


At follow-up



Patients: Chemotherapy refractory metastatic NSCLC (n=39)
Treatment: Radiotherapy and concurrent anti-CTLA-4 Ab

- 51 clones being present in tumor, 20/51 are not detected at baseline in blood and showing a significant expansion from baseline at any of the time points (day 22, day 43, day 64) during treatment in blood

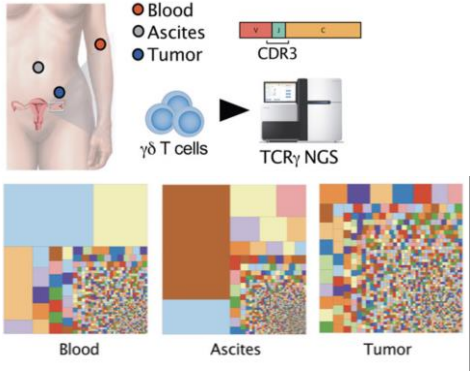


Formenti SC et al. Nat Med. 2018;24:1845-1851

More recent evidence of clinical association with TCRseq

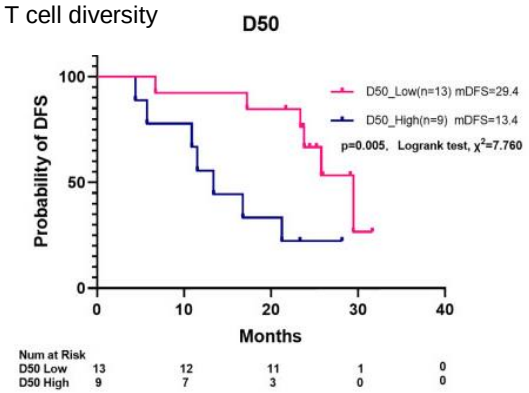
Characterization of ascites- and tumor-infiltrating γδ T cells reveals distinct repertoires and a beneficial role in ovarian cancer

Sci Transl Med. 2021;13:eabb0192.



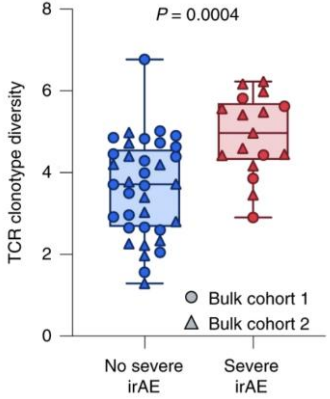
High TCR clonality (and % CD8⁺ T cells) as predictors of efficacy of neoadjuvant chemotherapy in breast cancer

Front Immunol. 2021;12:689091.



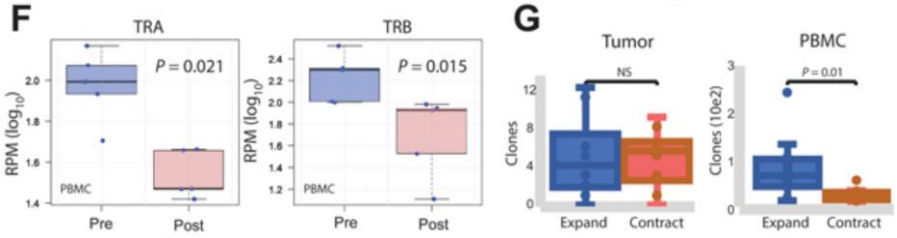
Pretreatment TCR diversity (and CD4⁺ T_{em}) in circulation is associated with severe immune-related adverse events after immune checkpoints

Nat Med. 2022.



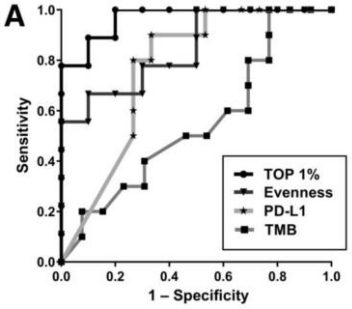
TCR sequencing changes in T-cell repertoire in peripheral blood with PD-L1+CTLA-4+Radiation for metastatic colorectal cancer

Clin Cancer Res. 2021;27:2470-2480



Pretreatment TCR evenness and top 1% clones outperform PD-L1 TPS and TMB as predictive biomarkers of complete pathological response after neoadjuvant chemo-immunotherapy in NSCLC

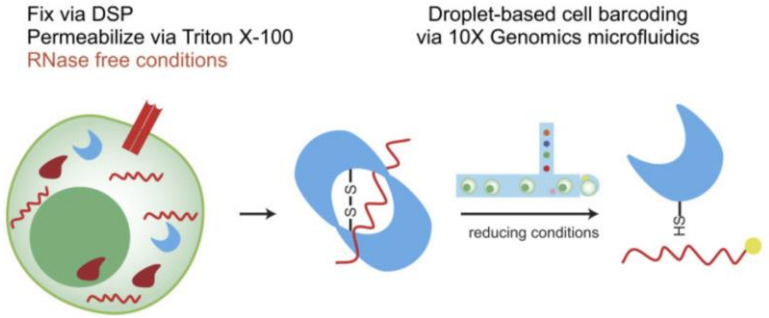
Clin Cancer Res. 2021;27:5878-5890



Recent technical advances (fixed cells, integration with GEX, AI)

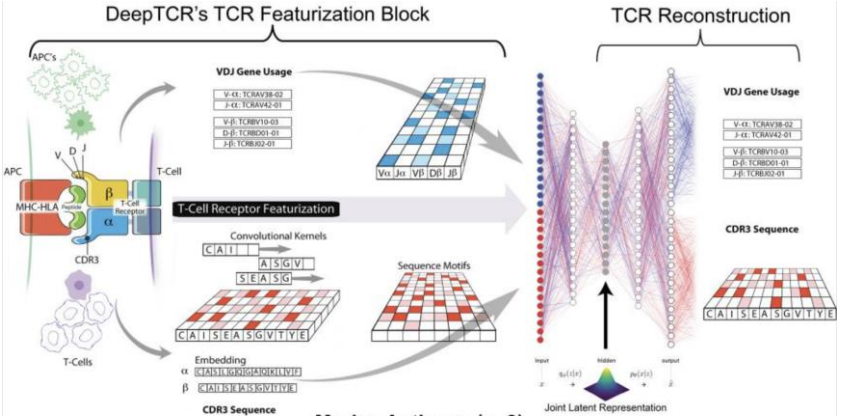
Droplet-based mRNA sequencing of fixed and permeabilized cells by CLInt-seq allows for antigen-specific TCR cloning with intracellular cytokine information

Proc Natl Acad Sci U S A. 2021;118(3):e2021190118



DeepTCR: a deep learning framework for revealing sequence concepts within T-cell repertoires (convolutional neural networks)

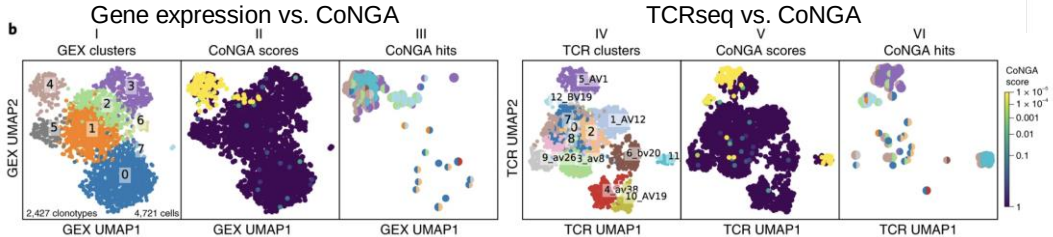
Nat Commun. 2021;12:1605.



Cluster antigen-specific TCRs better

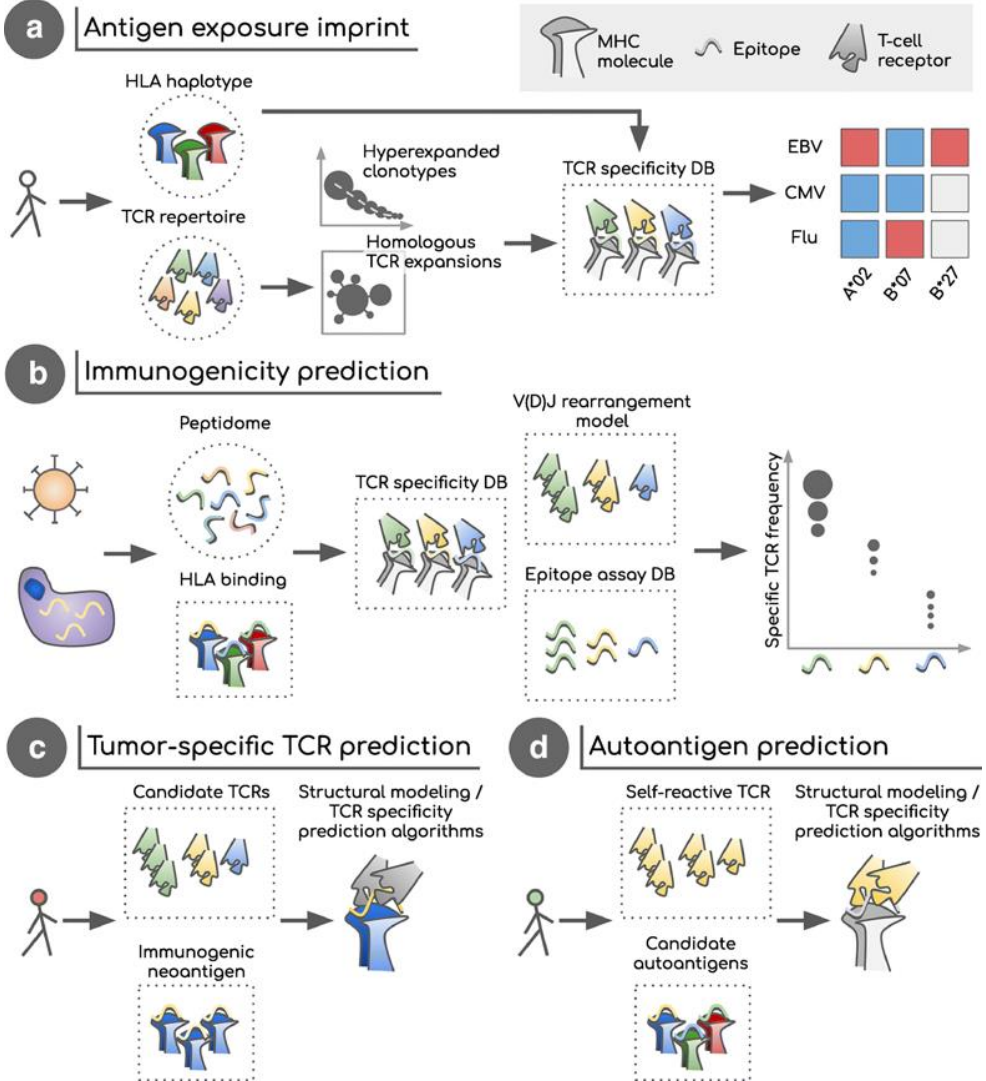
Integrating T cell receptor sequences and transcriptional profiles by clonotype neighbor graph analysis (CoNGA)

Nat Biotechnol. 2022;40:54-63



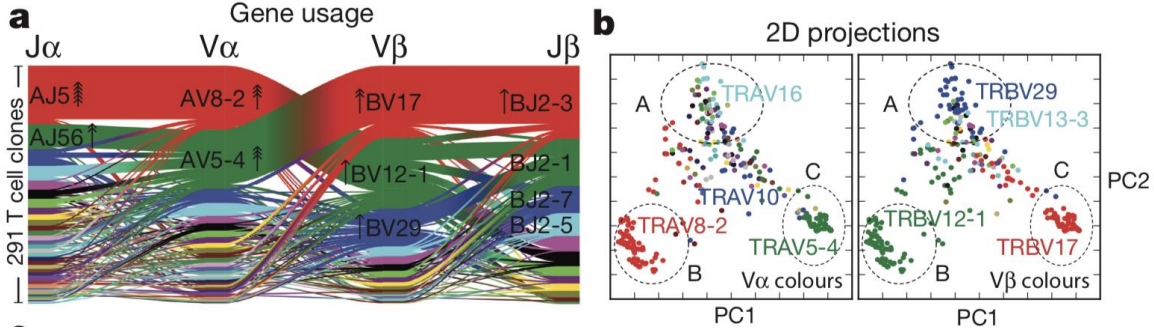
CoNGA identifies statistically significant overlap between a GEX similarity graph and a TCR sequence similarity graph

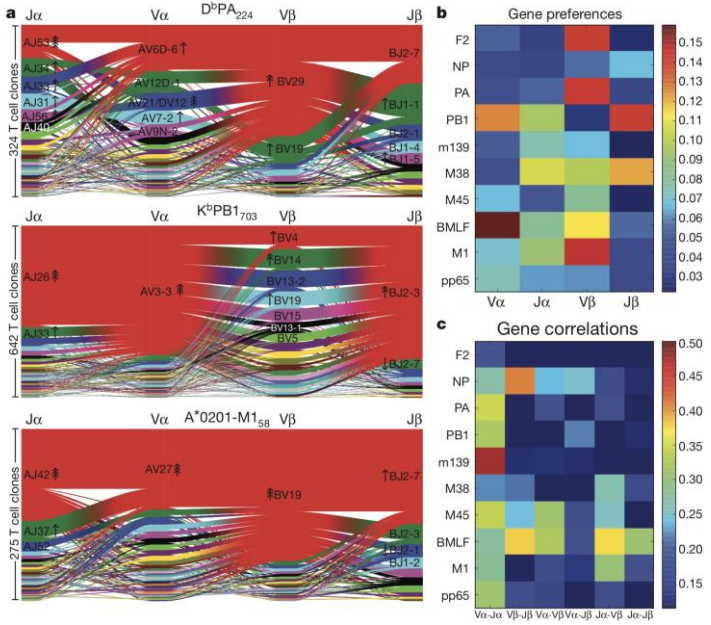
Querying TCR specificity

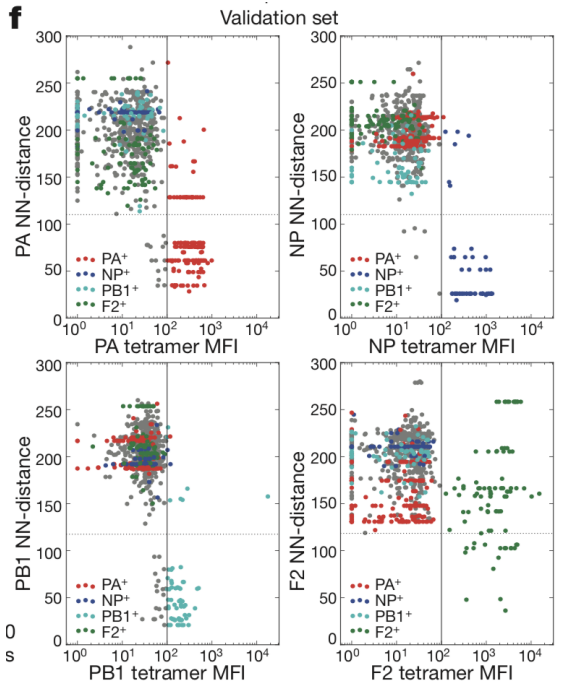


Zvyagin IV, Tsvetkov VO, Chudakov DM, Shugay M. Immunogenetics. 2019

Combine tetramer sorting with single-cell TCRseq to find clusters of related TCRs and metrics that can predict similar specificity



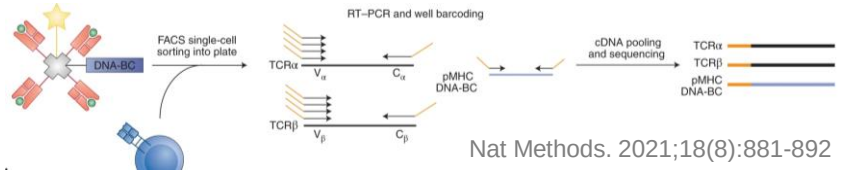




Dash et al. Nature 2017;547;89

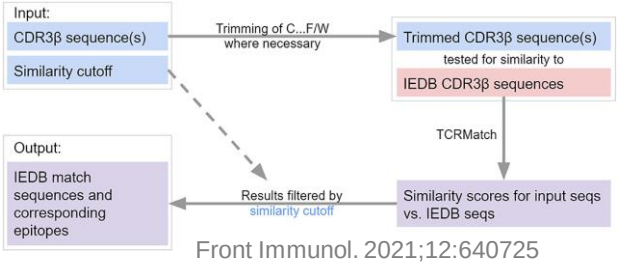
Predicting antigen specificity

Linking TCR sequence to antigen specificity using tetramers



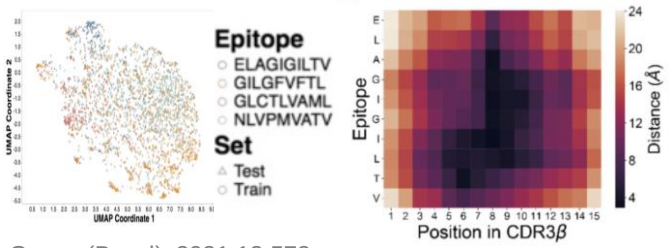
Nat Methods. 2021;18(8):881-892

TCRMatch: Predicting T-cell receptor specificity based on sequence similarity to previously characterized receptors



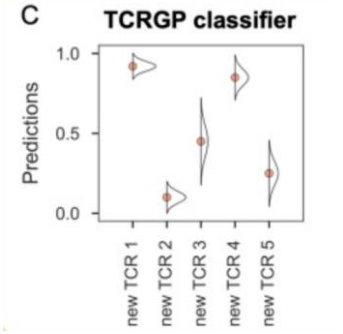
Front Immunol. 2021;12:640725

Neural network model to predict epitopes



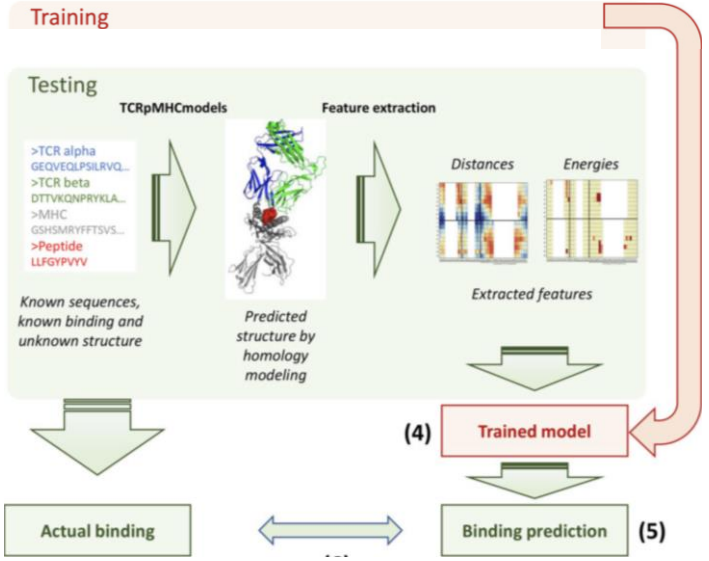
Genes (Basel). 2021;12:572

Training on known epitopes using Gaussian process

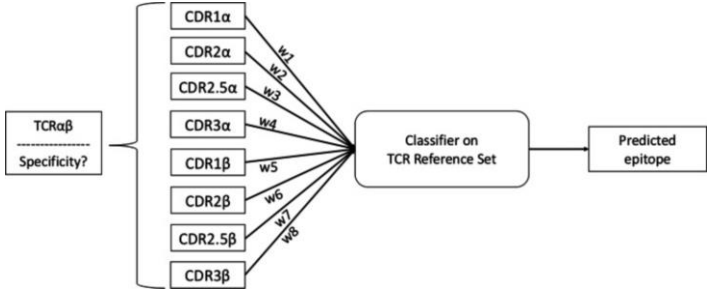


PLoS Comput Biol. 2021;17:e1008814

Based on homology models Front Physiol. 2021;12:730908

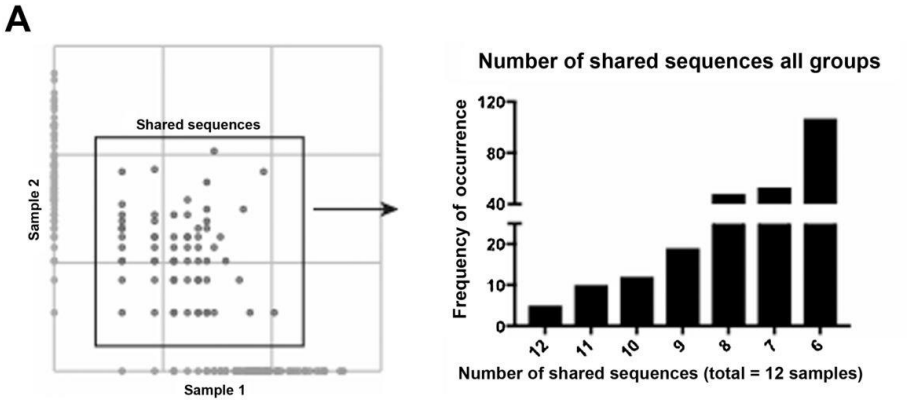


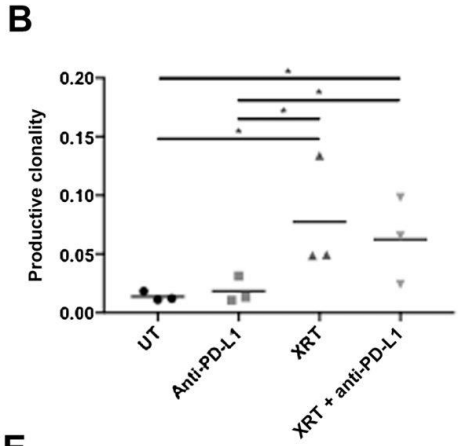
SwarmTCR: a computational approach



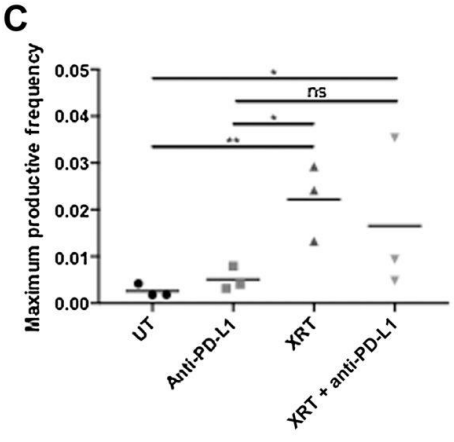
BMC Bioinformatics. 2021;22:422

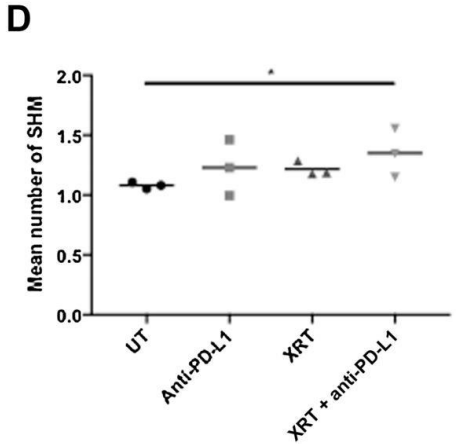
BCR sequencing as biomarker of cancer outcome still underexplored

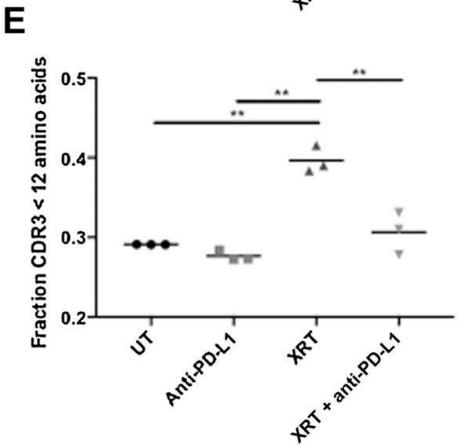




B cells associated with overall survival benefit in HPV+ squamous cell carcinomas and are activated by radiation and PD-1 blockade







BCR-sequencing found that radiotherapy enhances B cell clonality, decreases CDR3 length, and induces B-cell somatic hypermutation.

Clin Cancer Res. 2020;26:3345-3359.

Take home message

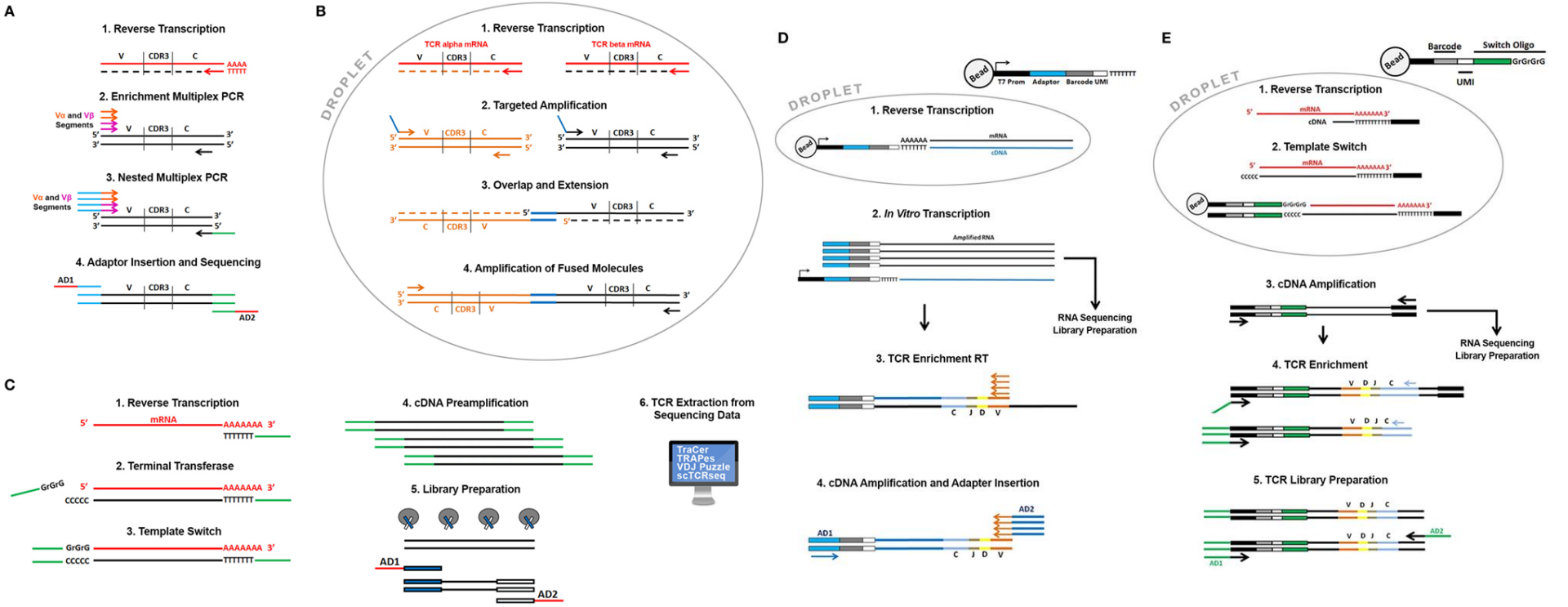
TCR and BCR sequencing provide important metrics of clonality/diversity of the adaptive immune repertoire of lymphocytes in cancer patients

Many papers showing predictive biomarker value for TCR repertoire in I-O trials

Flexibility of methods (bulk, single cell, survey, deep) from different materials (FFPE, blood, RNA, gDNA) allow for a wide variety of tissue sources

Choosing the approach depends on downstream need and tissue availability

TCR/BCR sequencing is a useful tool in the arsenal of immune monitoring technologies



Frontiers in Immunology. 2018;9:1638

Subgroup Gene Allele

α Genes

101 sequences

IMGT subgroup	IMGT gene name	IMGT allele name	Function
TRAV1	TRAV1-1	TRAV1-1*01	F
		TRAV1-1*02	(F)
	TRAV1-2	TRAV1-2*01	F
		TRAV1-2*02	(F)
TRAV2	TRAV2	TRAV2*01	F
		TRAV2*02	(F)
TRAV3	TRAV3	TRAV3*01	F
		TRAV3*02	(P)
TRAV4	TRAV4	TRAV4*01	F
TRAV5	TRAV5	TRAV5*01	F
TRAV6	TRAV6	TRAV6*01	F
		TRAV6*02	(F)
		TRAV6*03	(F)
		TRAV6*04	(F)
		TRAV6*05	(F)
		TRAV6*06	(F)
TRAV7	TRAV7	TRAV7*01	F
TRAV8	TRAV8-1	TRAV8-1*01	F
		TRAV8-1*02	(F)
	TRAV8-2	TRAV8-2*01	F
		TRAV8-2*02	(F)
	TRAV8-3	TRAV8-3*01	F
		TRAV8-3*02	(F)
		TRAV8-3*03	(F)
	TRAV8-4	TRAV8-4*01	F
		TRAV8-4*02	(F)
		TRAV8-4*03	(F)
		TRAV8-4*04	(F)
		TRAV8-4*05	(F)
		TRAV8-4*06	(F)
		TRAV8-4*07	(F)
	TRAV8-5	TRAV8-5*01	P
	TRAV8-6	TRAV8-6*01	F
		TRAV8-6*02	F
	TRAV8-7	TRAV8-7*01	ORF
TRAV9	TRAV9-1	TRAV9-1*01	F
	TRAV9-2	TRAV9-2*01	F
		TRAV9-2*02	(F)
		TRAV9-2*03	(F)
		TRAV9-2*04	(F)
TRAV10	TRAV10	TRAV10*01	F
TRAV11	TRAV11	TRAV11*01	P
TRAV12	TRAV12-1	TRAV12-1*01	F
		TRAV12-1*02	(F)
	TRAV12-2	TRAV12-2*01	F
		TRAV12-2*02	(F)
		TRAV12-2*03	(F)
	TRAV12-3	TRAV12-3*01	F
		TRAV12-3*02	(F)
TRAV13	TRAV13-1	TRAV13-1*01	F
		TRAV13-1*02	(F)
		TRAV13-1*03	(F)
	TRAV13-2	TRAV13-2*01	F
		TRAV13-2*02	(F)
TRAV14	TRAV14DV4	TRAV14DV4*01	F
		TRAV14DV4*02	F
		TRAV14DV4*03	(F)
		TRAV14DV4*04	(F)
TRAV15	TRAV15	TRAV15*01	P
TRAV16	TRAV16	TRAV16*01	F
TRAV17	TRAV17	TRAV17*01	F
TRAV18	TRAV18	TRAV18*01	F
TRAV19	TRAV19	TRAV19*01	F
TRAV20	TRAV20	TRAV20*01	F
		TRAV20*02	(F)
		TRAV20*03	(F)
		TRAV20*04	(F)
TRAV21	TRAV21	TRAV21*01	F
		TRAV21*02	(F)
TRAV22	TRAV22	TRAV22*01	F
TRAV23	TRAV23DV6	TRAV23DV6*01	F
		TRAV23DV6*02	(F)
		TRAV23DV6*03	(F)
		TRAV23DV6*04	(F)
TRAV24	TRAV24	TRAV24*01	F
		TRAV24*02	(F)
TRAV25	TRAV25	TRAV25*01	F
TRAV26	TRAV26-1	TRAV26-1*01	F
		TRAV26-1*02	(F)
		TRAV26-1*03	(F)
	TRAV26-2	TRAV26-2*01	F
		TRAV26-2*02	(F)
TRAV27	TRAV27	TRAV27*01	F
		TRAV27*02	(F)
		TRAV27*03	(F)
TRAV28	TRAV28	TRAV28*01	P
TRAV29	TRAV29DV5	TRAV29DV5*01	F
		TRAV29DV5*02	(F)
		TRAV29DV5*03	P
TRAV30	TRAV30	TRAV30*01	F
		TRAV30*02	(F)
		TRAV30*03	(F)
		TRAV30*04	(F)
TRAV31	TRAV31	TRAV31*01	P
TRAV32	TRAV32	TRAV32*01	P
TRAV33	TRAV33	TRAV33*01	P
TRAV34	TRAV34	TRAV34*01	F
TRAV35	TRAV35	TRAV35*01	F
		TRAV35*02	(F)
TRAV36	TRAV36DV7	TRAV36DV7*01	F
		TRAV36DV7*02	(F)
		TRAV36DV7*03	(F)
		TRAV36DV7*04	(F)
TRAV37	TRAV37	TRAV37*01	P
TRAV38	TRAV38-1	TRAV38-1*01	F
		TRAV38-1*02	(F)
		TRAV38-1*03	(F)
		TRAV38-1*04	(F)
	TRAV38-2/DV8	TRAV38-2/DV8*01	F
		TRAV38-2/DV8*02	F
		TRAV38-2/DV8*03	F
		TRAV38-2/DV8*04	F
TRAV39	TRAV39	TRAV39*01	F
TRAV40	TRAV40	TRAV40*01	F
TRAV41	TRAV41	TRAV41*01	F

β Genes

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IMGT subgroup	IMGT gene name	IMGT allele name	Function
TRBV1	TRBV1	TRBV1*01	P
TRBV2	TRBV2	TRBV2*01	F
		TRBV2*02	(P)
		TRBV2*03	(P)
TRBV3	TRBV3-1	TRBV3-1*01	F
		TRBV3-1*02	(P)
	TRBV3-2	TRBV3-2*01	P
		TRBV3-2*02	P
		TRBV3-2*03	(P)
TRBV4	TRBV4-1	TRBV4-1*01	F
		TRBV4-1*02	(P)
	TRBV4-2	TRBV4-2*01	F
		TRBV4-2*02	(P)
	TRBV4-3	TRBV4-3*01	F
		TRBV4-3*02	(P)
		TRBV4-3*03	(P)
		TRBV4-3*04	(P)
TRBV5	TRBV5-1	TRBV5-1*01	P
		TRBV5-1*02	(P)
	TRBV5-2	TRBV5-2*01	(P)
	TRBV5-3	TRBV5-3*01	ORF
		TRBV5-3*02	ORF
	TRBV5-4	TRBV5-4*01	F
		TRBV5-4*02	(P)
		TRBV5-4*03	(P)
		TRBV5-4*04	(P)
	TRBV5-5	TRBV5-5*01	F
		TRBV5-5*02	(P)
		TRBV5-5*03	(P)
	TRBV5-6	TRBV5-6*01	F
	TRBV5-7	TRBV5-7*01	ORF
	TRBV5-8	TRBV5-8*01	F
		TRBV5-8*02	(P)
TRBV6	TRBV6-1	TRBV6-1*01	F
		TRBV6-1*02	F
	TRBV6-2	TRBV6-2*01	(P)
		TRBV6-2*02	(P)
	TRBV6-3	TRBV6-3*01	F
	TRBV6-4	TRBV6-4*01	F
	TRBV6-5	TRBV6-5*01	F
		TRBV6-5*02	F
	TRBV6-6	TRBV6-6*01	(P)
		TRBV6-6*02	(P)
		TRBV6-6*03	(P)
		TRBV6-6*04	(P)
		TRBV6-6*05	(P)
	TRBV6-7	TRBV6-7*01	ORF
	TRBV6-8	TRBV6-8*01	F
	TRBV6-9	TRBV6-9*01	F
TRBV7	TRBV7-1	TRBV7-1*01	ORF
	TRBV7-2	TRBV7-2*01	F
		TRBV7-2*02	F
		TRBV7-2*03	F
		TRBV7-2*04	(P)
	TRBV7-3	TRBV7-3*01	F
		TRBV7-3*02	ORF
		TRBV7-3*03	ORF
		TRBV7-3*04	(P)
		TRBV7-3*05	(P)
	TRBV7-4	TRBV7-4*01	F
		TRBV7-4*02	(P)
	TRBV7-5	TRBV7-5*01	P
		TRBV7-5*02	P
	TRBV7-6	TRBV7-6*01	F
		TRBV7-6*02	(P)
	TRBV7-7	TRBV7-7*01	F
		TRBV7-7*02	(P)
	TRBV7-8	TRBV7-8*01	F
		TRBV7-8*02	F
		TRBV7-8*03	(P)
	TRBV7-9	TRBV7-9*01	F
		TRBV7-9*02	(P)
		TRBV7-9*03	P
		TRBV7-9*04	(P)
		TRBV7-9*05	(P)
		TRBV7-9*06	(P)
		TRBV7-9*07	(P)
TRBV8	TRBV8-1	TRBV8-1*01	P
	TRBV8-2	TRBV8-2*01	P
TRBV9	TRBV9	TRBV9*01	F
		TRBV9*02	F
		TRBV9*03	(P)
TRBV10	TRBV10-1	TRBV10-1*01	F
		TRBV10-1*02	F
		TRBV10-1*03	(P)
	TRBV10-2	TRBV10-2*01	F
		TRBV10-2*02	(P)
	TRBV10-3	TRBV10-3*01	F
		TRBV10-3*02	F
		TRBV10-3*03	(P)
TRBV11	TRBV11-1	TRBV11-1*01	F
		TRBV11-1*02	F
	TRBV11-2	TRBV11-2*01	F
		TRBV11-2*02	(P)
		TRBV11-2*03	(P)
	TRBV11-3	TRBV11-3*01	(P)
		TRBV11-3*02	(P)
		TRBV11-3*03	(P)
		TRBV11-3*04	(P)
TRBV12	TRBV12-1	TRBV12-1*01	P
	TRBV12-2	TRBV12-2*01	P
	TRBV12-3	TRBV12-3*01	F
		TRBV12-3*02	F
	TRBV12-4	TRBV12-4*01	F
		TRBV12-4*02	(P)
	TRBV12-5	TRBV12-5*01	F
TRBV13	TRBV13	TRBV13*01	F
		TRBV13*02	(P)
TRBV14	TRBV14	TRBV14*01	F
		TRBV14*02	(P)
TRBV15	TRBV15	TRBV15*01	F
		TRBV15*02	(P)
		TRBV15*03	(P)
TRBV16	TRBV16	TRBV16*01	P
		TRBV16*02	(P)
TRBV17	TRBV17	TRBV17*01	ORF
TRBV18	TRBV18	TRBV18*01	F
TRBV19	TRBV19	TRBV19*01	F
		TRBV19*02	F
		TRBV19*03	(P)
TRBV20	TRBV20-1	TRBV20-1*01	F
		TRBV20-1*02	F
		TRBV20-1*03	(P)
		TRBV20-1*04	(P)
		TRBV20-1*05	(P)
		TRBV20-1*06	(P)
TRBV21	TRBV21-1	TRBV21-1*01	P
TRBV22	TRBV22-1	TRBV22-1*01	P
TRBV23	TRBV23-1	TRBV23-1*01	ORF
TRBV24	TRBV24-1	TRBV24-1*01	F
TRBV25	TRBV25-1	TRBV25-1*01	F
TRBV26	TRBV26	TRBV26*01	P
TRBV27	TRBV27	TRBV27*01	F
TRBV28	TRBV28	TRBV28*01	F
TRBV29	TRBV29-1	TRBV29-1*01	F
		TRBV29-1*02	(F)
		TRBV29-1*03	(F)
TRBV30	TRBV30	TRBV30*01	F
		TRBV30*02	P
		TRBV30*03	P
		TRBV30*04	(P)
		TRBV30*05	(P)