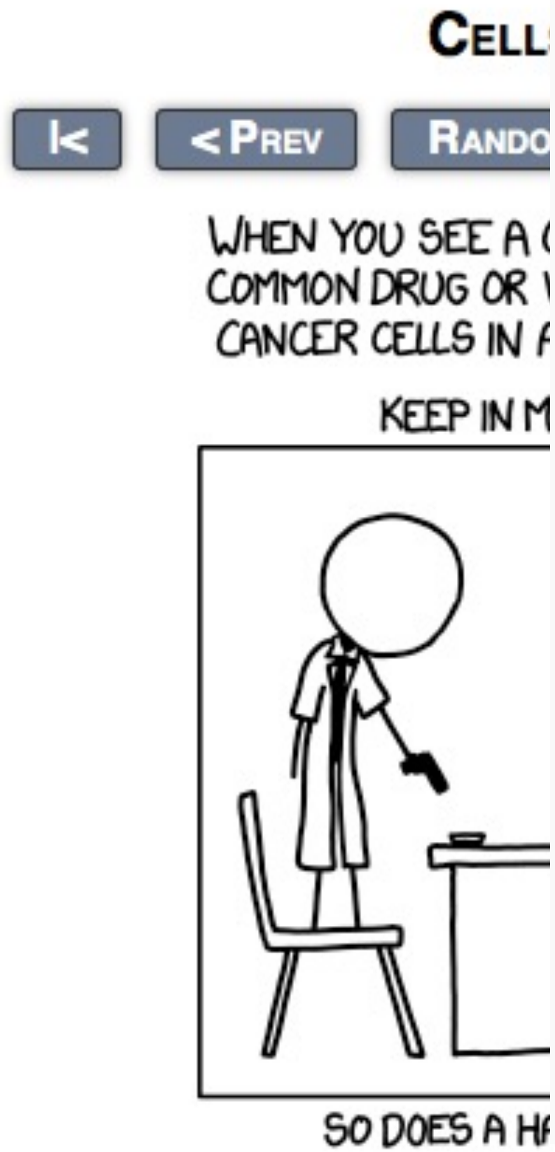
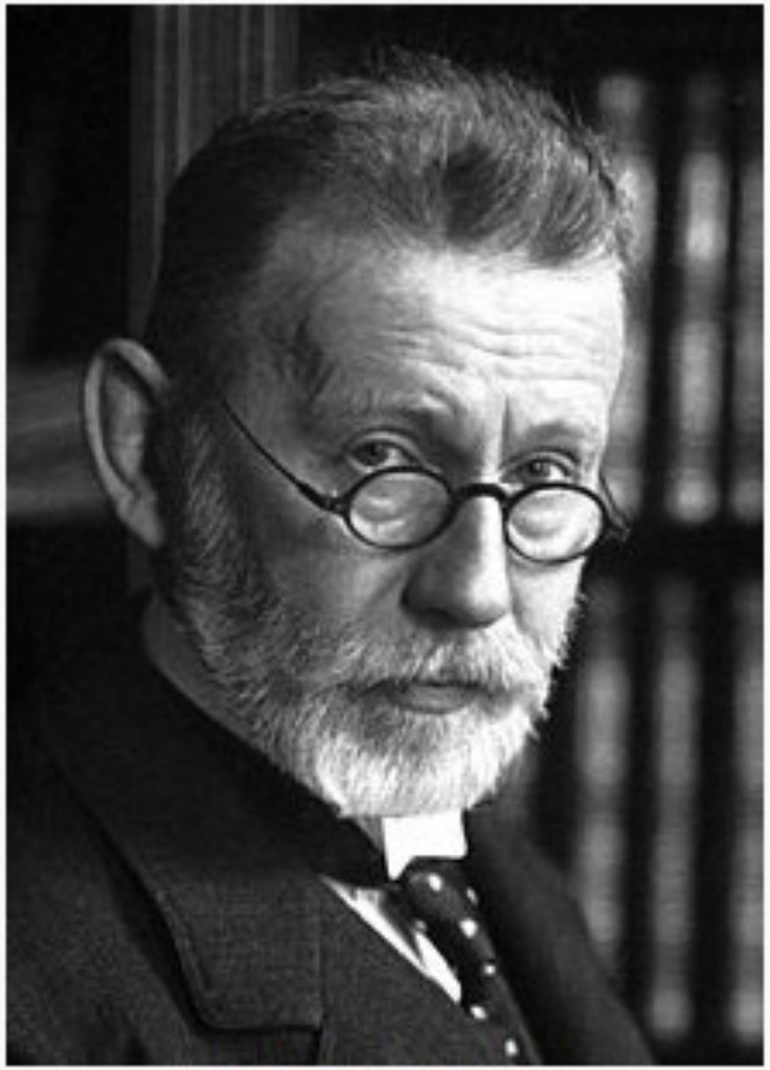
Computational Approaches to Target Identification for Cellular Therapy

Benjamin Vincent, MD
UNC Hematology | Microbiology & Immunology | Bioinformatics & Computational Biology | Computational Medicine

Cancer specific therapy is an obvious goal…





Paul Ehrlich c. 1908

"We must learn to aim and to aim in a chemical sense." - Paul Ehrlich (1854 - 1915)

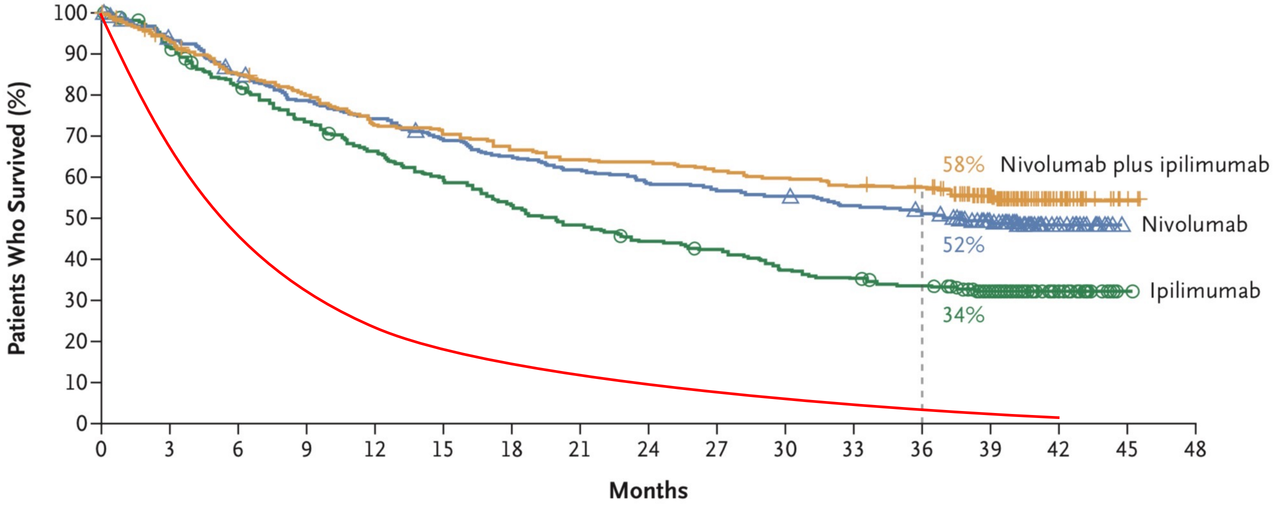
Munroe R, http://xkcd.com/1217; www.wikipedia.org

Survival in the Age of Immunotherapy

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma



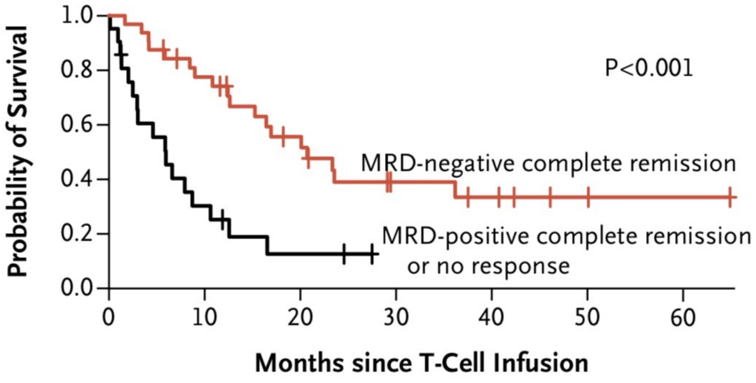
Wolchok J et al. (2017) *NEJM* 377:1345

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

D Overall Survival, According to MRD Status and Response



No. at Risk

MRD-negative complete response	32	23	14	7	5	2	1
MRD-positive complete response or no response	21	6	2	0	0	0	0

Park JH et al. (2018) *NEJM* 378:449

Our Goal is Cure

2018 ASCO® ANNUAL MEETING

DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

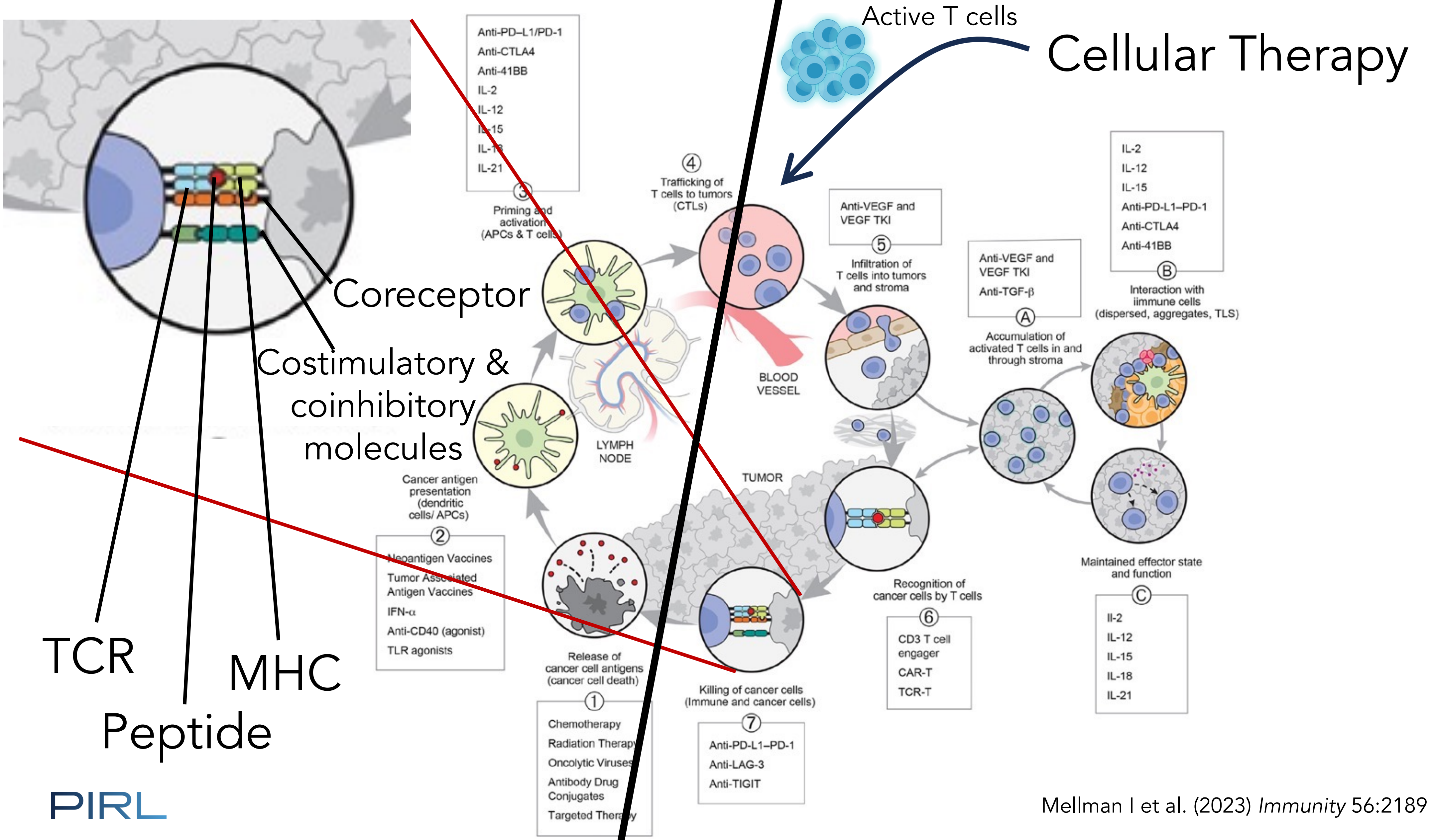
National Cancer Institute (NCI)
29,209 followers
2mo

NCI Director Dr. Sharpless highlights research findings from the 2018 ASCO meeting.

Of course, we don't want to overpromise and give people, especially patients, false hope. But too many from my generation are afraid to be optimistic, too sheepish to ever use the word "cure." But that's what we want to do, *cure* our patients. We are, in fact, curing patients right now, more than ever, including those with metastatic cancer.

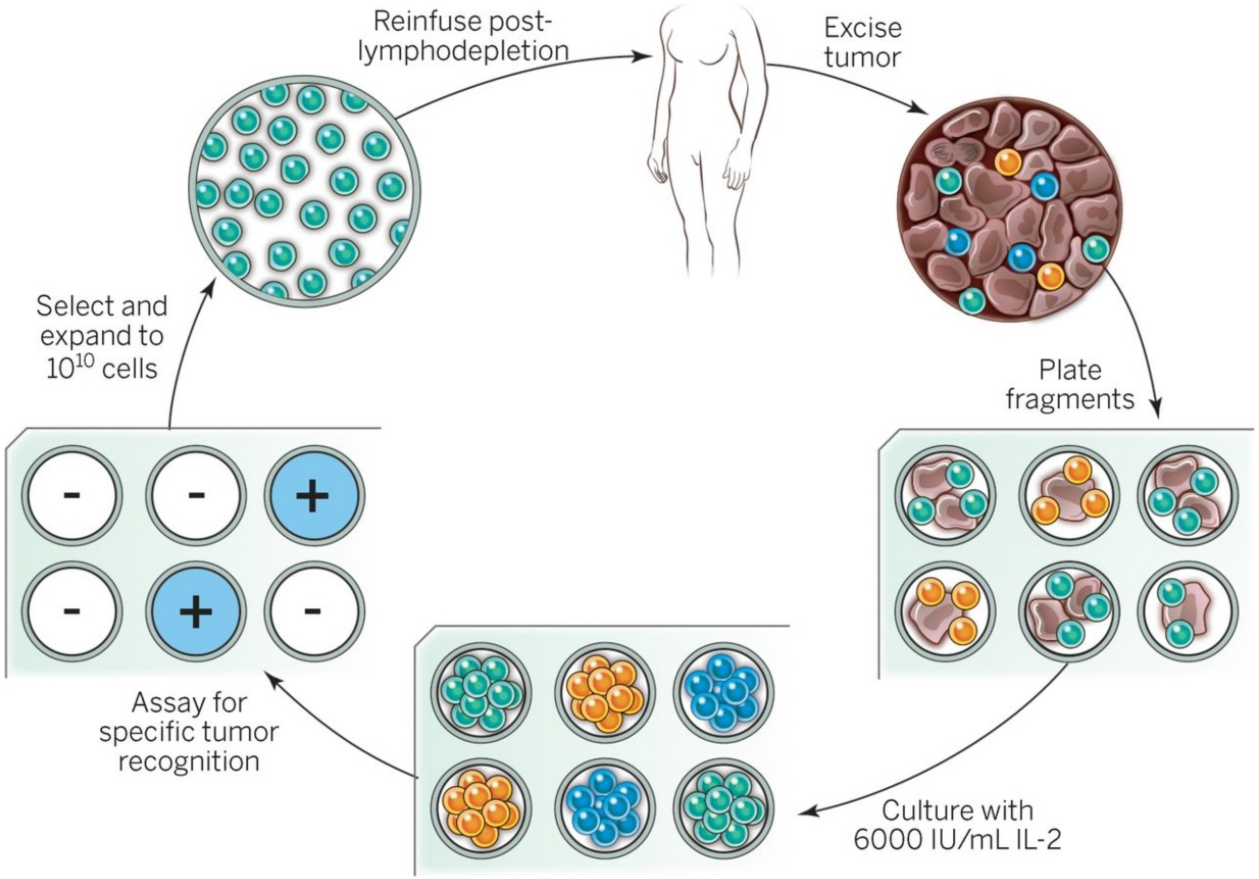
Thank you SITC

The Cancer Immunity Cycle



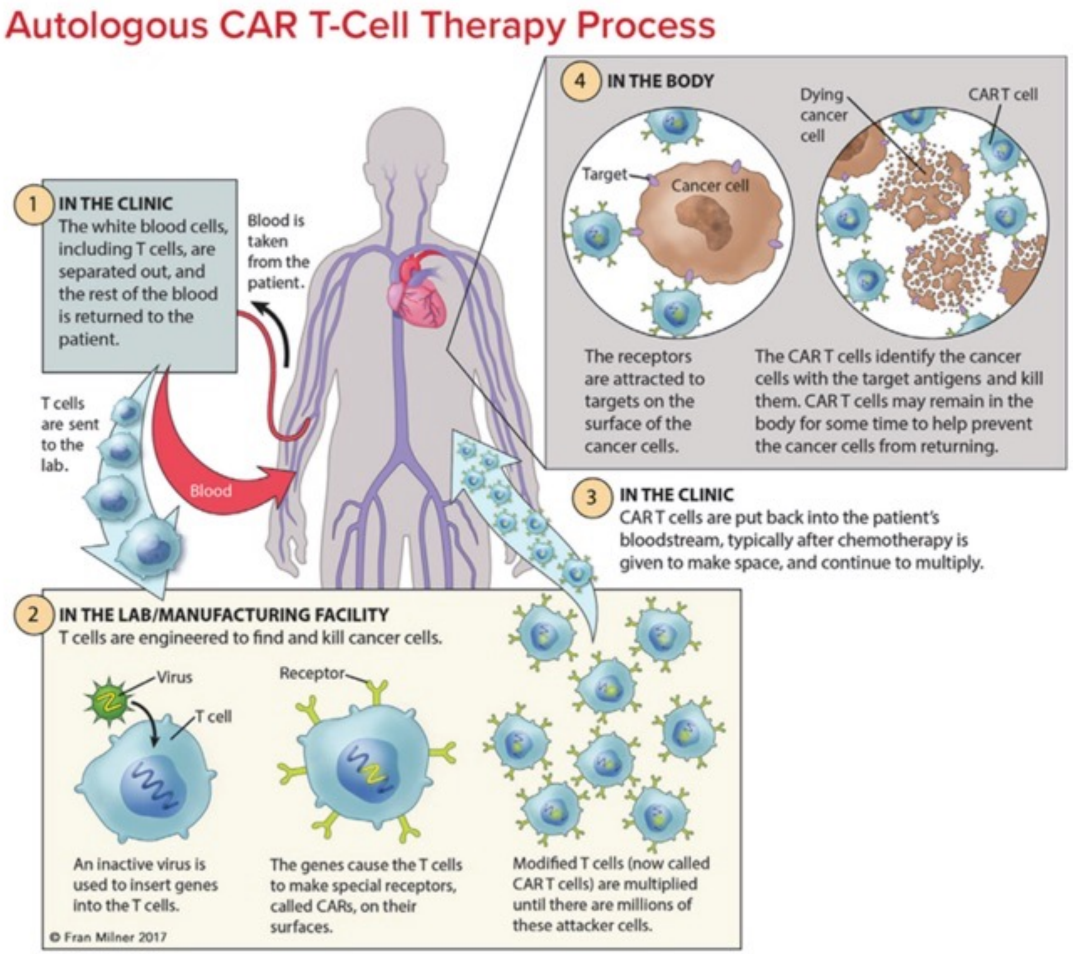
Two broad classes of cellular therapy

Endogenous T cells



Restifo N et al (2015) *Science*

Engineered T cells



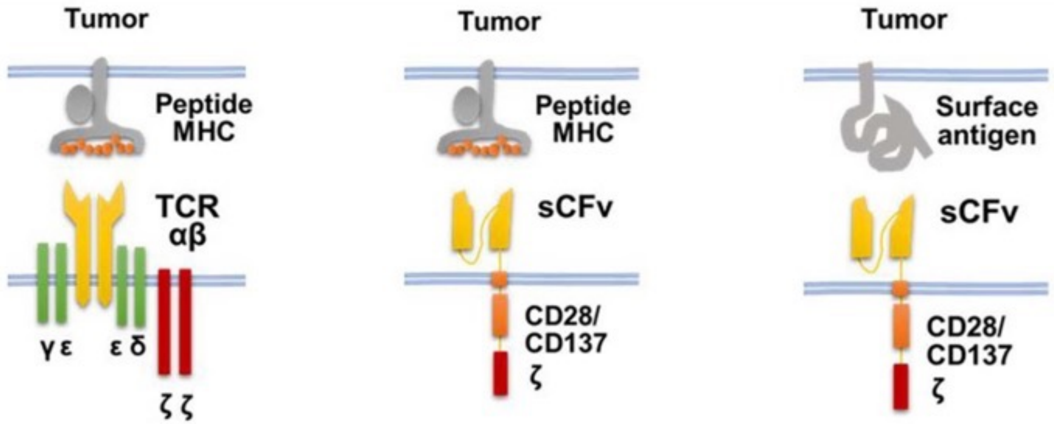
https://www.lls.org/treatment/types-treatment

CAR-T versus TCR-dependent T cell therapy

	TCR-T	TCR-like CAR-T	Conventional CAR-T
Receptor	T-cell receptor heterodimer	Single-chain variable fragment (scFv) from antibody	Single-chain variable fragment (scFv) from antibody
Target antigen	Peptide/MHC complex (intracellular protein)	Peptide/MHC complex (intracellular protein)	Cell surface antigen
MHC restriction	Dependent	Dependent	Independent
Minimal number of antigen per cell	1	Not fully studied, but 100<	100<
Range of receptor affinity (Kd)	$10^{-4} \sim 10^{-6}$ M	$10^{-6} \sim 10^{-9}$ M	$10^{-6} \sim 10^{-9}$ M
Costimulatory molecules	CD28, CD137	Linked directly to scFv (CD28 and/or CD137 in combination with CD3ζ)	Linked directly to scFv (CD28 and/or CD137 in combination with CD3ζ)
Corecptors	CD4 for MHC-II, CD8 for MHC-I	Unknown, some involvement of CD8 for MHC-I	Not fully studied
Serial killing function	Yes	Yes	Yes
Administration	One infusion	One infusion	Once infusion
Challenges	Cell manufacturing, competition to endogenouse TCR	Cell manufacturing	Cell manufacturing

Advantage TCR-T

Advantage CAR-T



PIRL

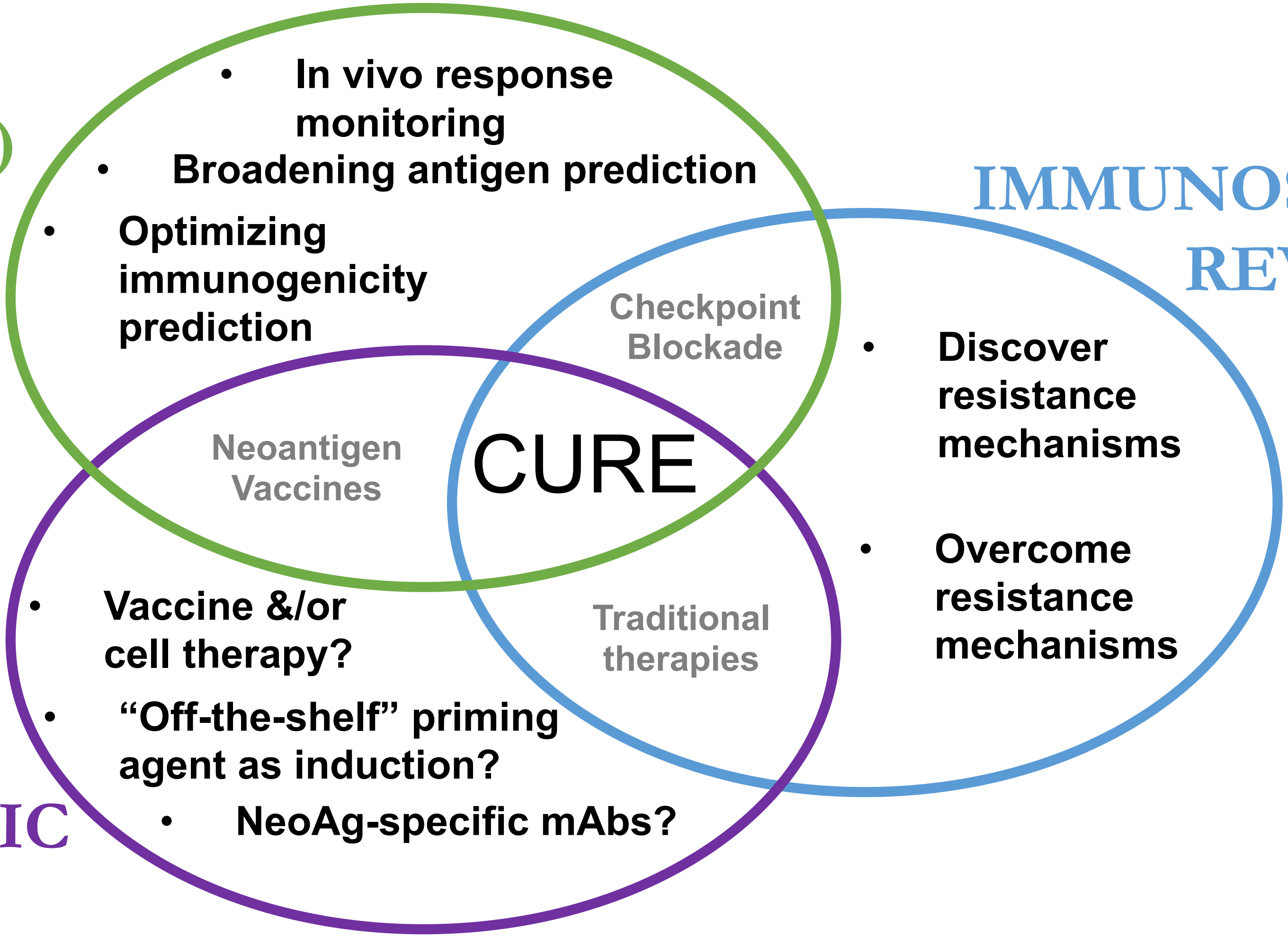
Akatsuka Y (2020) *Front Immunol.*11:257

UNC SCHOOL OF MEDICINE

Need to solve three problems for curative immunotherapy

TARGET ANTIGEN(S)

THERAPEUTIC AGENT(S)



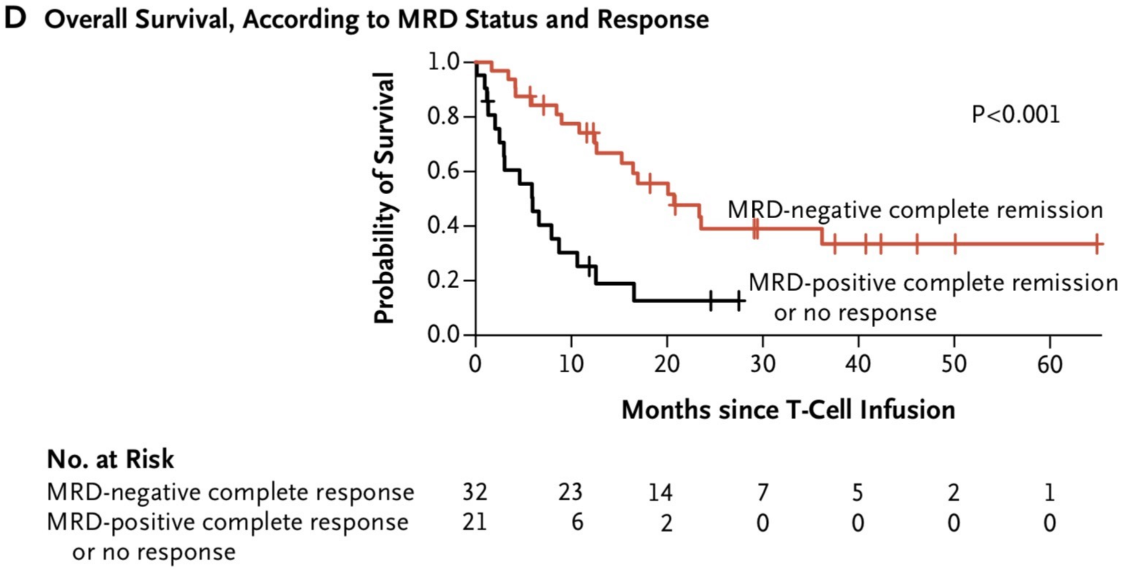
IMMUNOSUPPRESSION REVERSAL

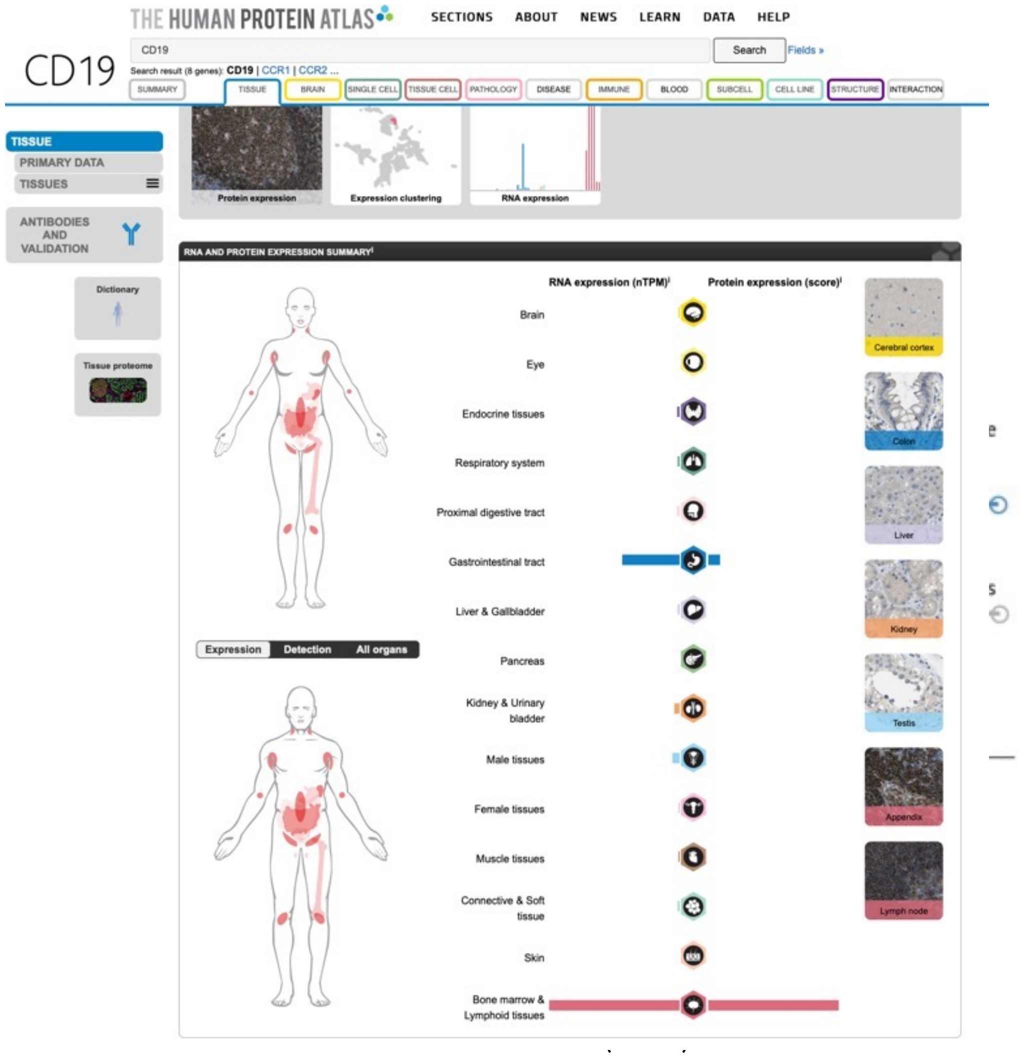
Impressive results with CD19-directed CAR-T therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

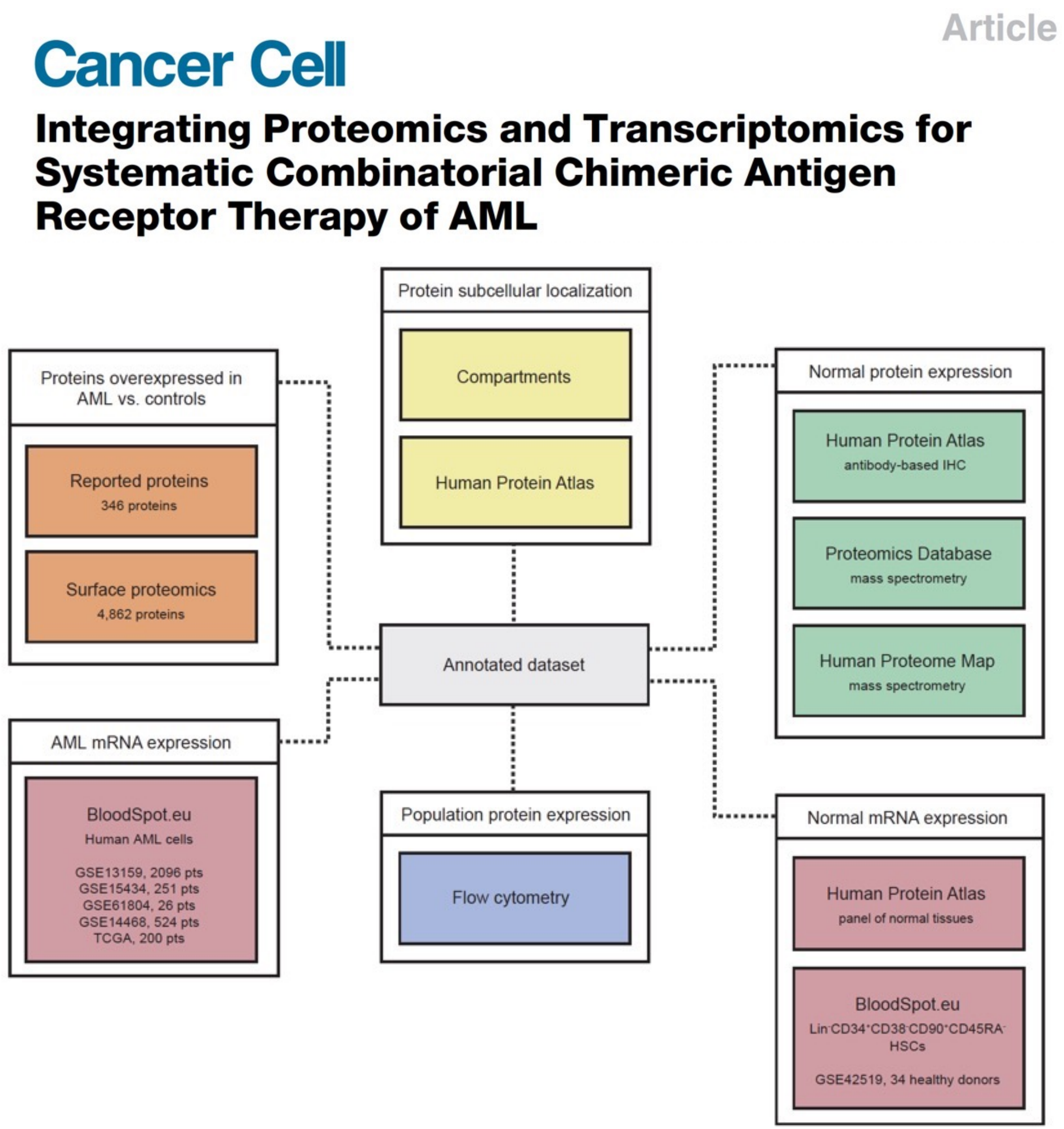
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

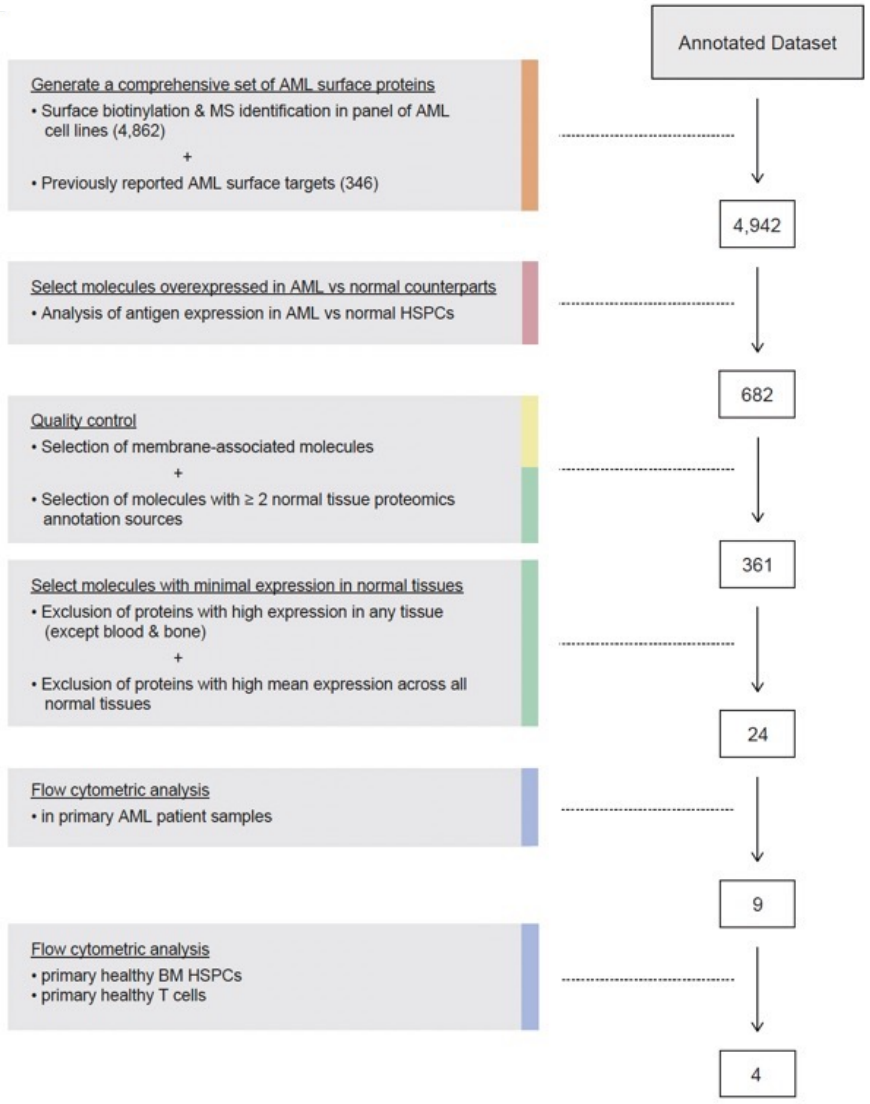




Park JH et al. (2018) *NEJM* 378:449

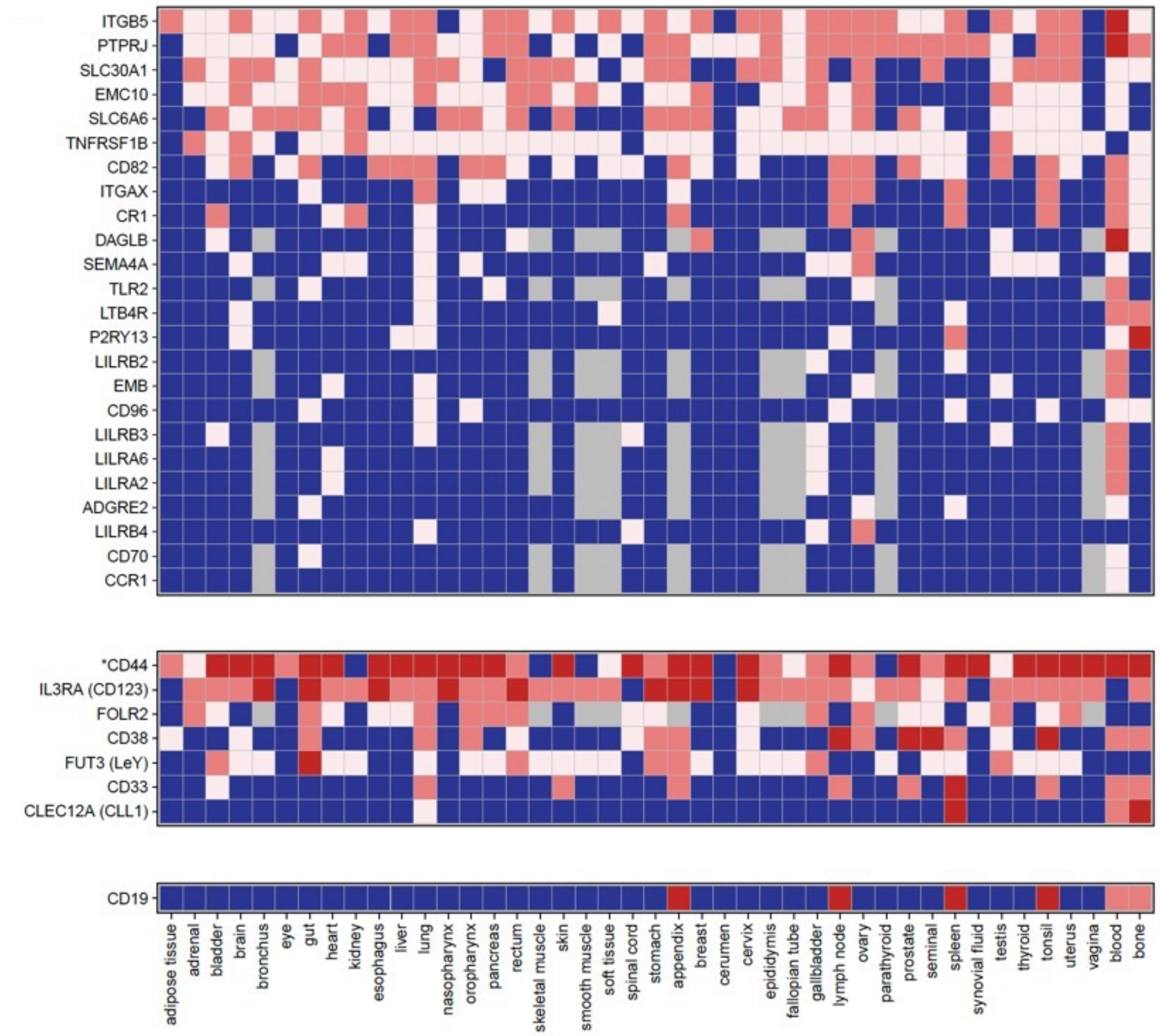
Finding good cell surface targets for CAR-T therapy

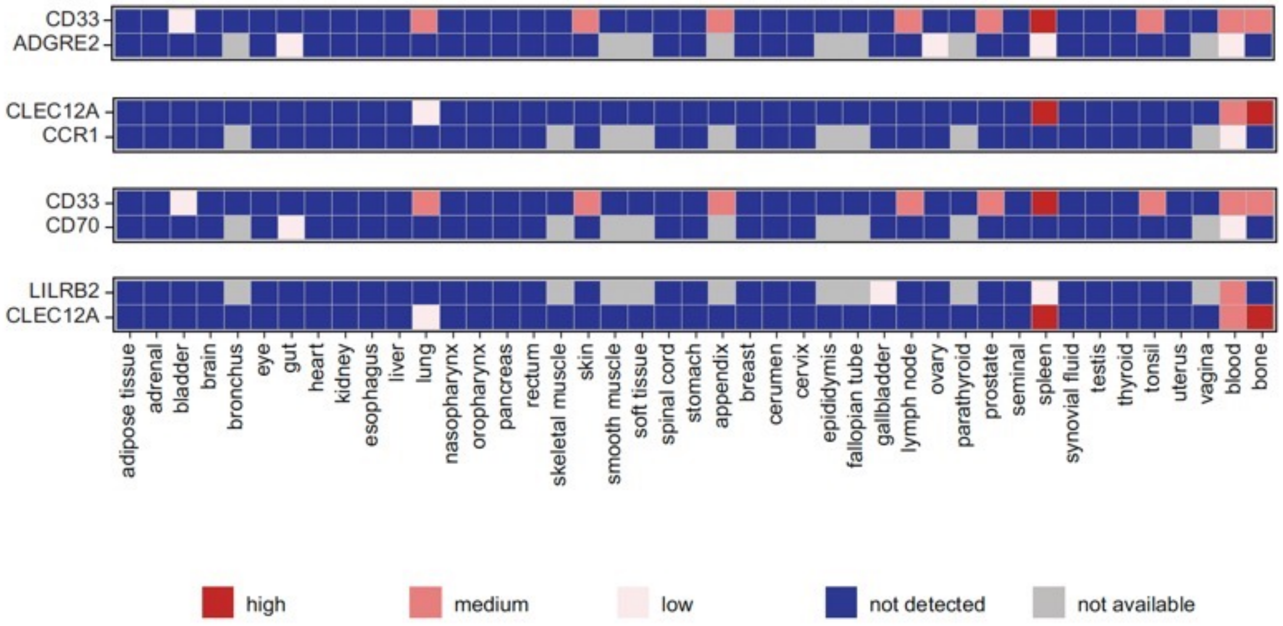




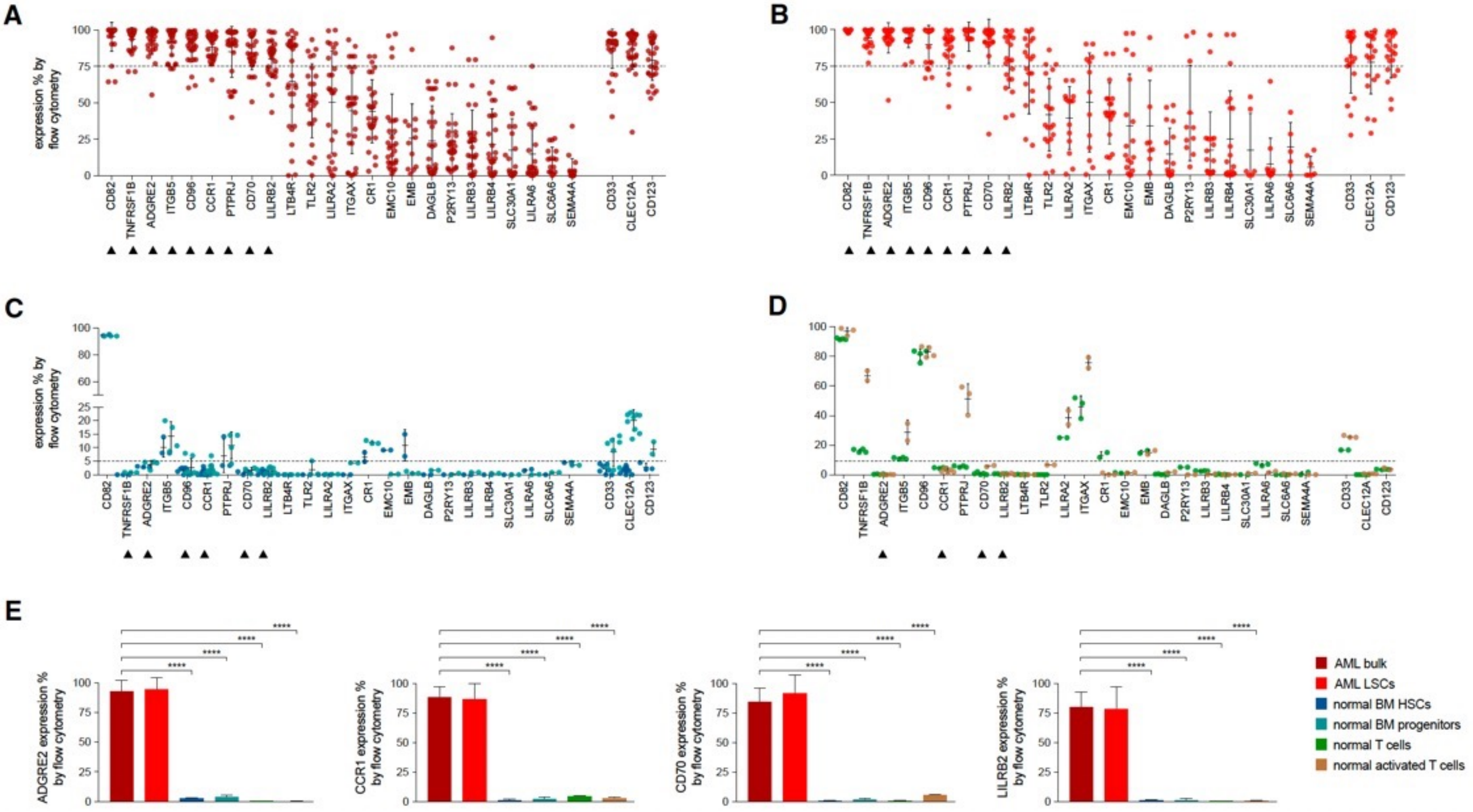
Perna F (2017) *Cancer Cell* 32:506

Potential cell surface target expression in AML



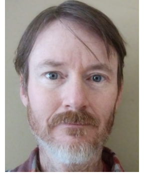


Potential cell surface target expression in AML



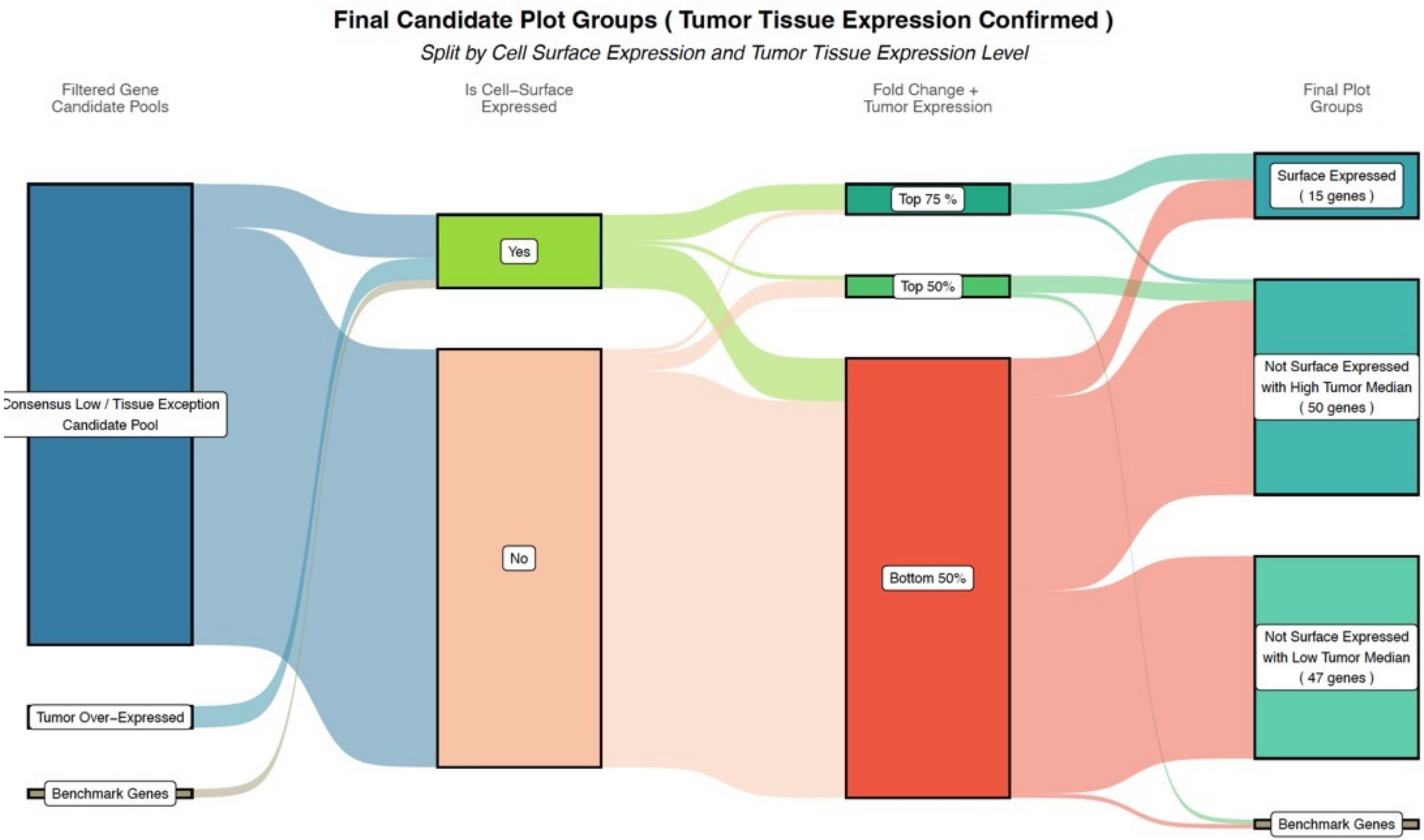
Perna F (2017) *Cancer Cell* 32:506

CAR-T target search in triple negative breast cancer



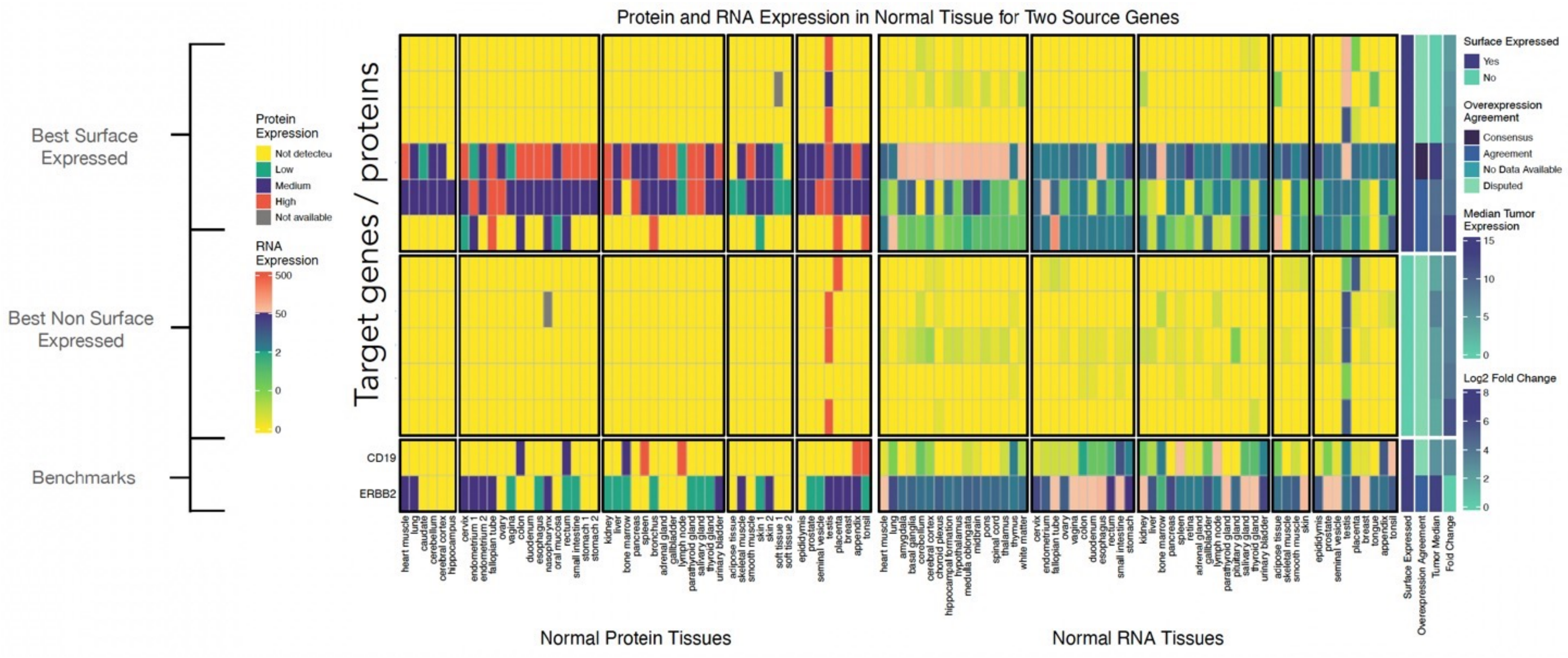
Nathan Wheeler

Dante Bortone

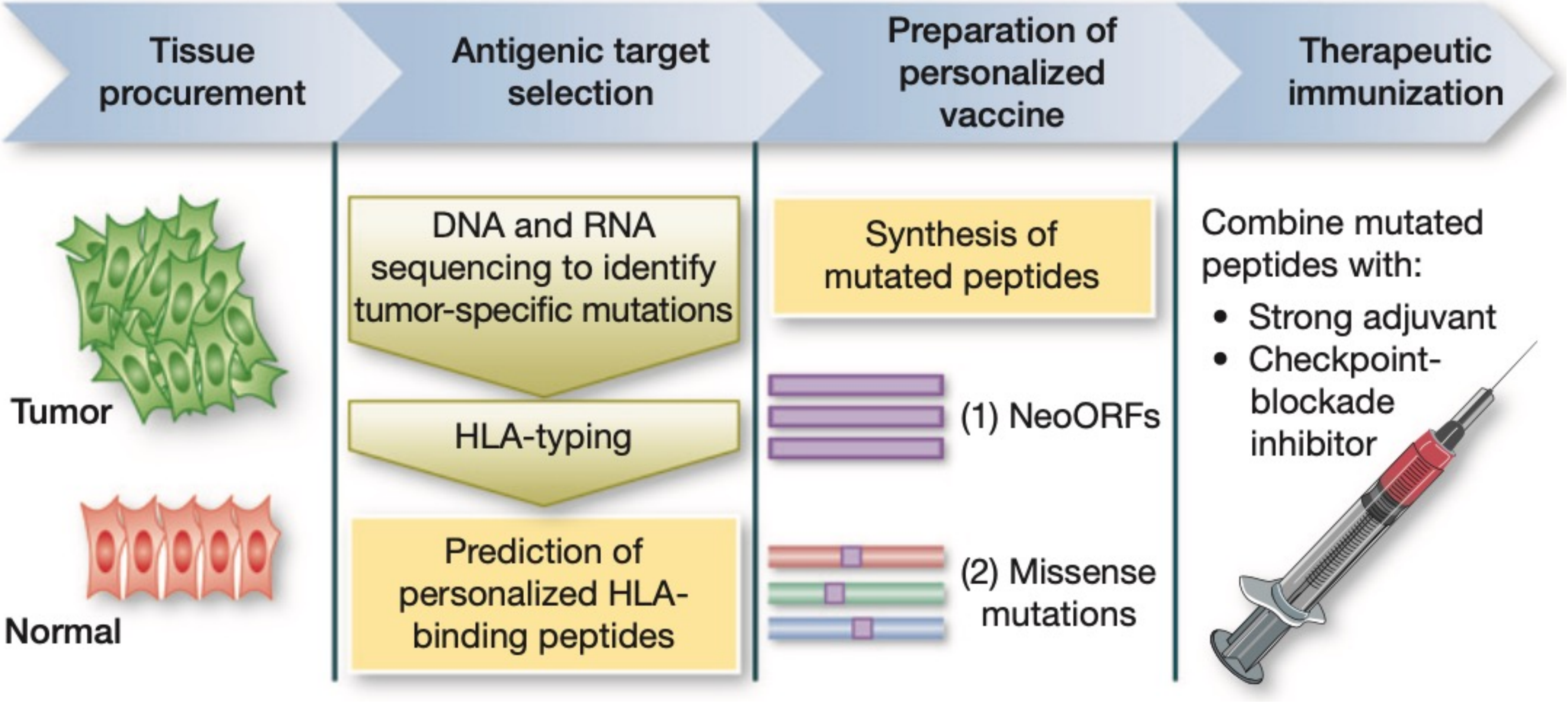


Unpublished data

CAR-T target search in triple negative breast cancer



Basic process for personalized neoantigen vaccine design



Hacohen et al (2013) Cancer Immunology Research 1(1):12

TCR-dependent target identification empowers personalized neoantigen vaccines

LETTER

doi:10.1038/nature10755

Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting

Hirokazu Matsushita[1]†*, Matthew D. Vesely[1]*, Daniel C. Koboldt[2], Charles G. Rickert[1], Ravindra Uppaluri[3], Vincent J. Magrini[2,4], Cora D. Arthur[1], J. Michael White[1], Yee-Shiuan Chen[1], Lauren K. Shea[1], Jasreet Hundal[2], Michael C. Wendl[2,4], Ryan Demeter[2], Todd Wylie[2], James P. Allison[5,6], Mark J. Smyth[7,8], Lloyd J. Old[9], Elaine R. Mardis[2,4] & Robert D. Schreiber[1]

Matsushita et al. (2012) *Nature* 378:449

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A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells

Beatriz M. Carreno,[1]* Vincent Magrini,[2] Michelle Becker-Hapak,[1] Saghar Kaabinejadian,[3] Jasreet Hundal,[2] Allegra A. Petti,[2] Amy Ly,[2] Wen-Rong Lie,[4] William H. Hildebrand,[3] Elaine R. Mardis,[2] Gerald P. Linette[1]

Carreno et al. (2015) *Science* 348(6236):803

Cancer Research

Microenvironment and Immunology

Exploiting the Mutanome for Tumor Vaccination

John C. Castle[1], Sebastian Kreiter[1], Jan Diekmann[1], Martin Löwer[1], Niels van de Roemer[1,2], Jos de Graaf[1], Abderraouf Selmi[1], Mustafa Diken[1], Sebastian Boegel[1,2], Claudia Paret[1], Michael Koslowski[1], Andreas N. Kuhn[1,3], Cedrik M. Britten[2,3], Christoph Huber[1,3], Özlem Türeci[4], and Ugur Sahin[1,2,3]

Castle J et al. (2012) *Cancer Research* 72(5):1081

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LETTER

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3]* & Özlem Türeci[8]*

Sahin U et al. (2017) *Nature* 547:222

Systematic identification of personal tumor-specific neoantigens in chronic lymphocytic leukemia

Mohini Rajasagi,[1,2] Sachet A. Shukla,[1,3] Edward F. Fritsch,[1,3] Derin B. Keskin,[1,2] David DeLuca,[1,3] Ellese Carmona,[4] Wandi Zhang,[1,2] Carrie Sougnez,[3] Kristian Cibulskis,[3] John Sidney,[5] Kristen Stevenson,[6] Jerome Ritz,[1,2,7] Donna Neuberg,[6] Vladimir Brusic,[1] Stacey Gabriel,[3] Eric S. Lander,[3] Gad Getz,[3,8] Nir Hacohen,[3,9] and Catherine J. Wu[1,2,7]

Rajasagi P et al. (2014) *Blood* 124(3)::453

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LETTER

doi:10.1038/nature22991

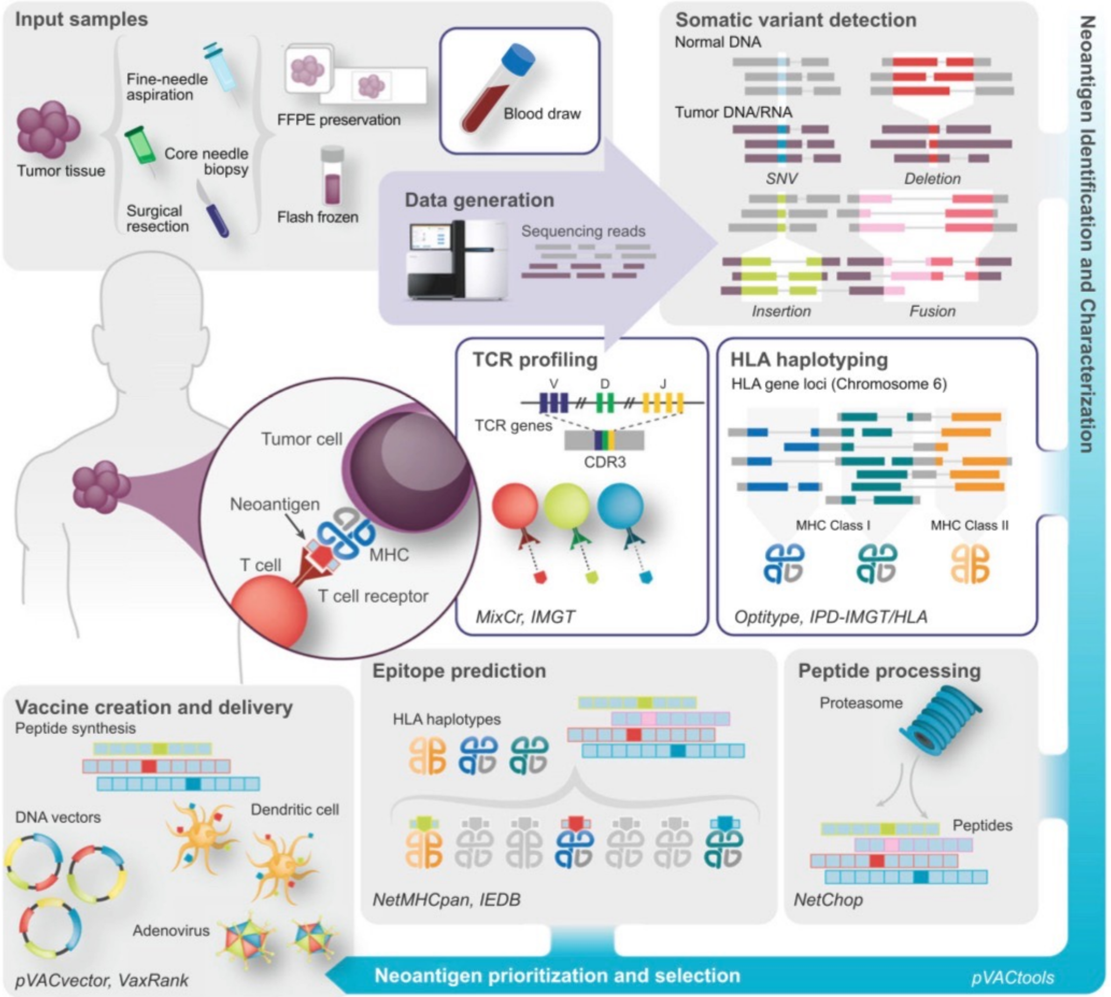
An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3]*, Zhuting Hu[1]*, Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[7], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4]†, Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

Ott P et al. (2017) *Nature* 547:217

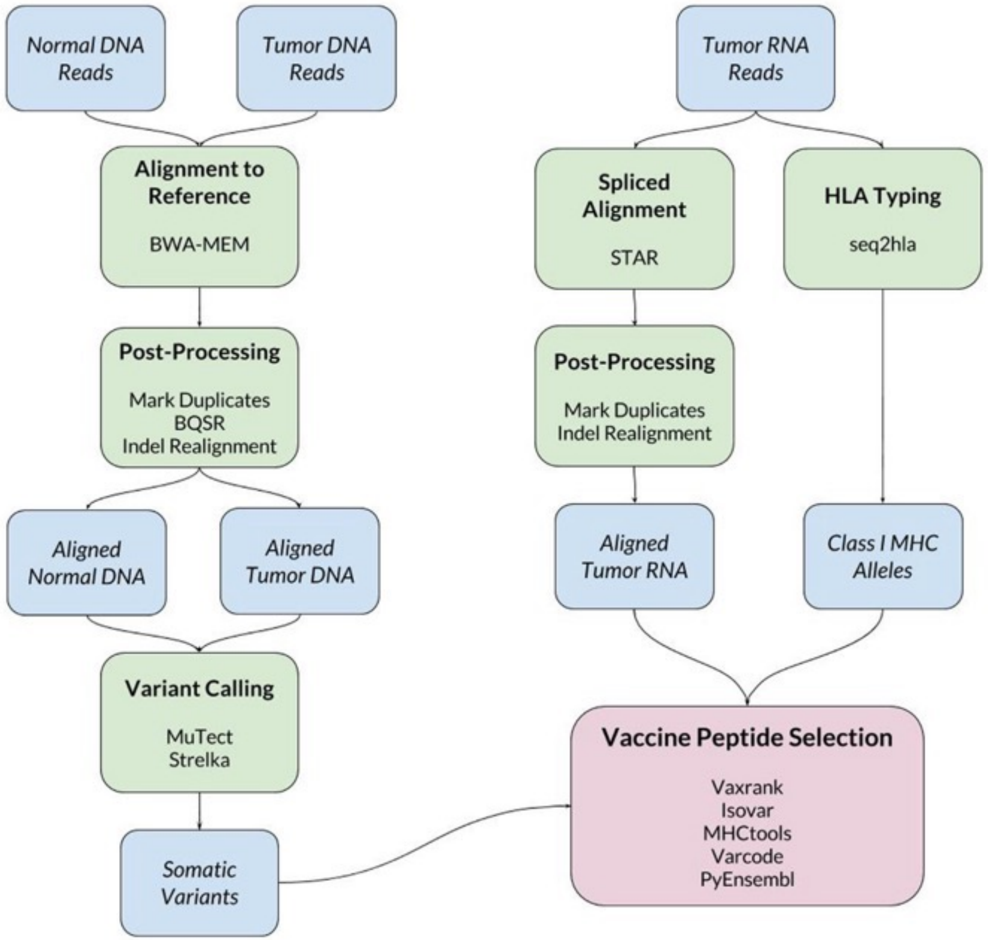
First open source neoantigen prediction workflows

pVACtools



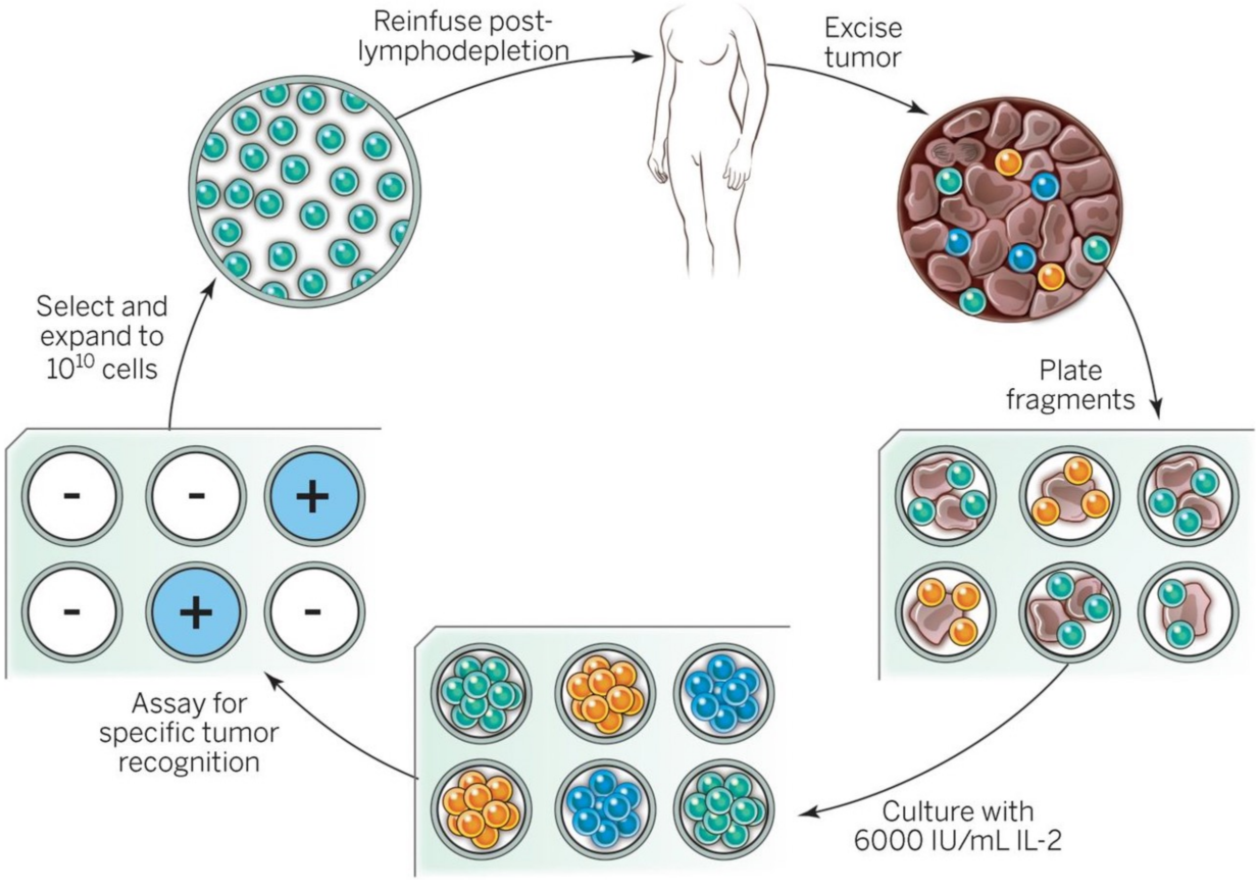
Richters M et al. (2019) *Genome Medicine* 11:56

OpenVax

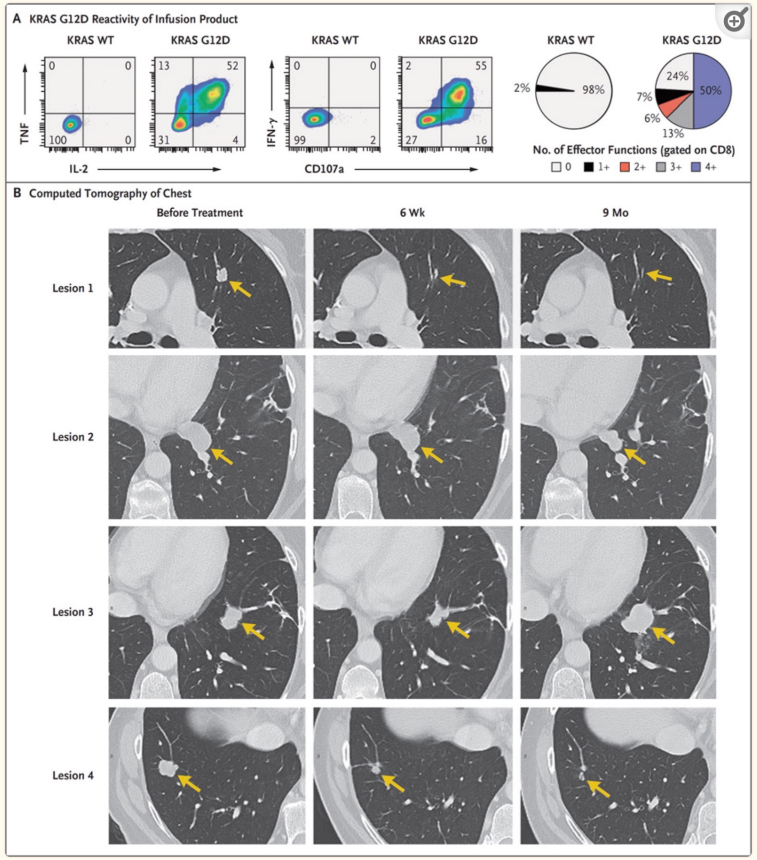


Rubinsteyn A et al. (2018) *Front Immunol* 8:1807

Targeting mutant KRAS with tumor-infiltrating T cell therapy



Restifo N et al (2015) *Science*



BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

Tran E et al (2016) *NEJM*

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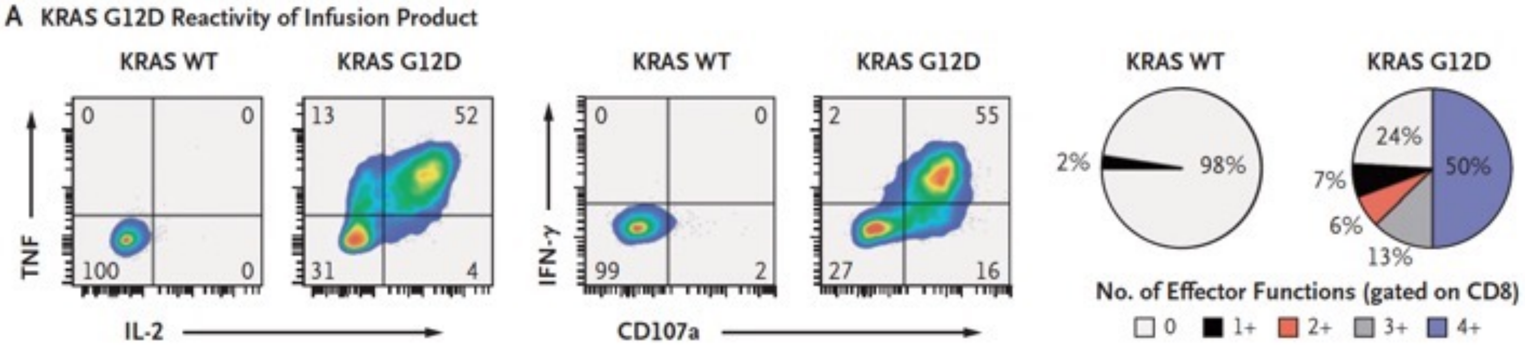
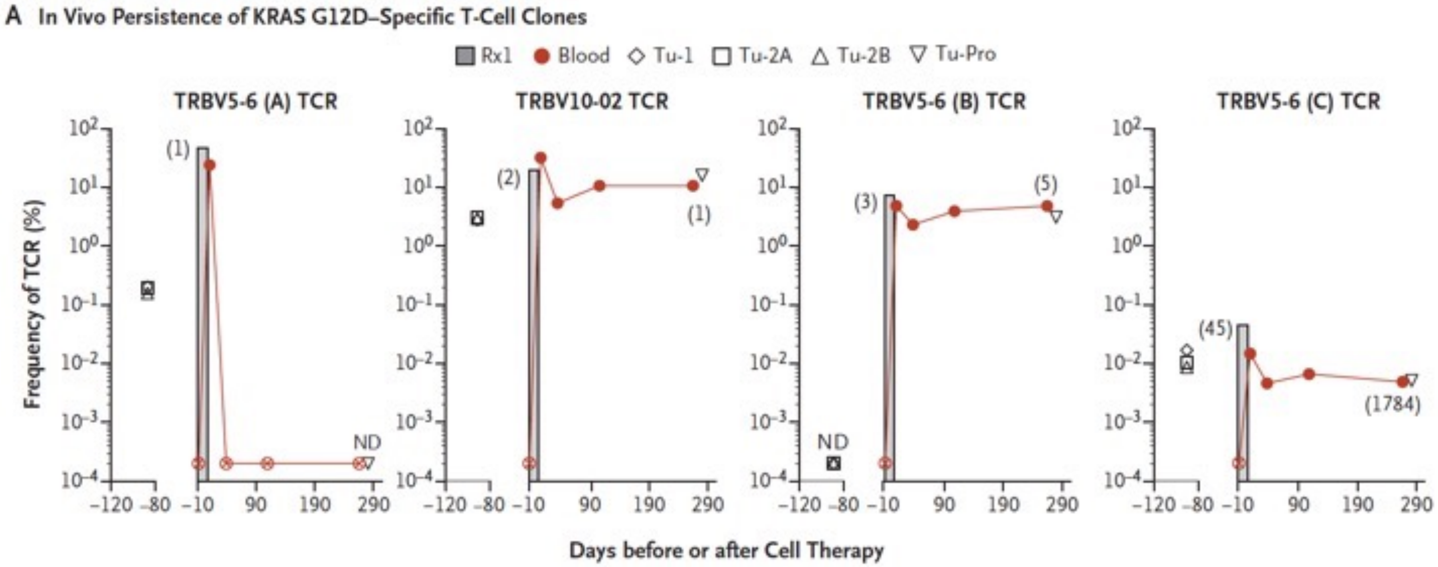
Targeting mutant KRAS with tumor-infiltrating T cell therapy

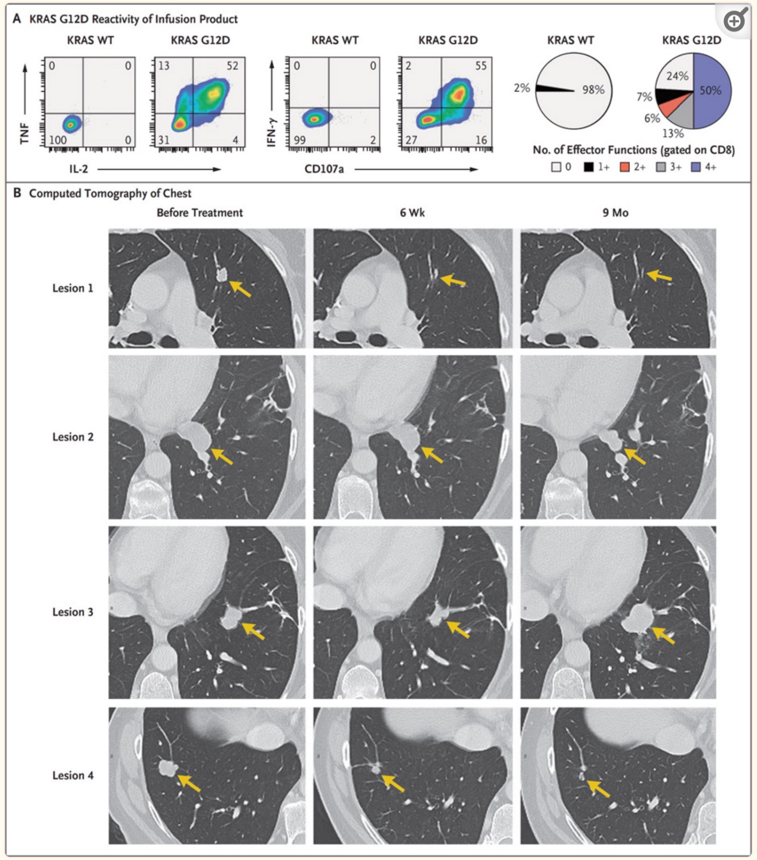




BRIEF REPORT

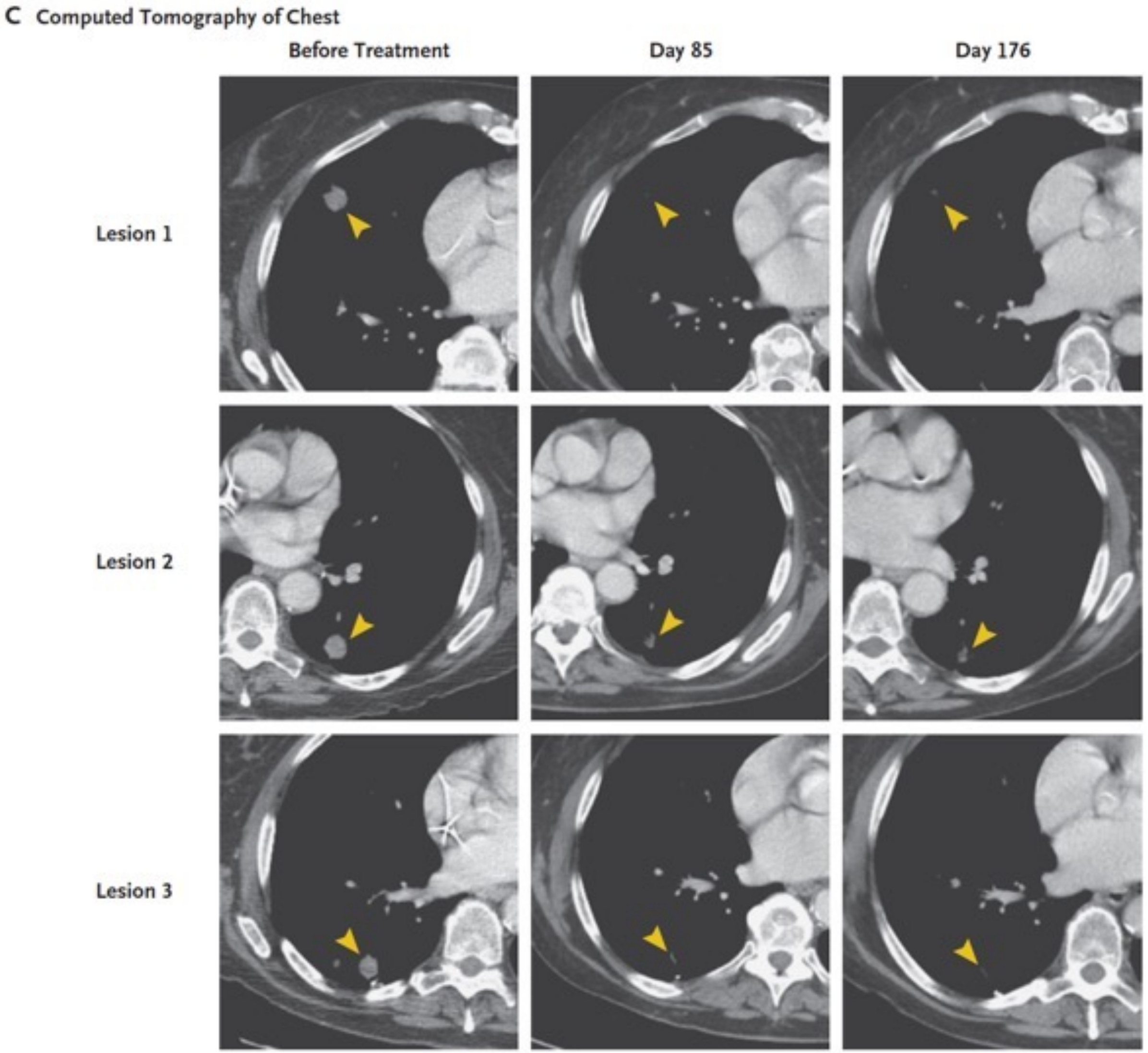
T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.



Tran E et al (2016) *NEJM* 375(23):2255

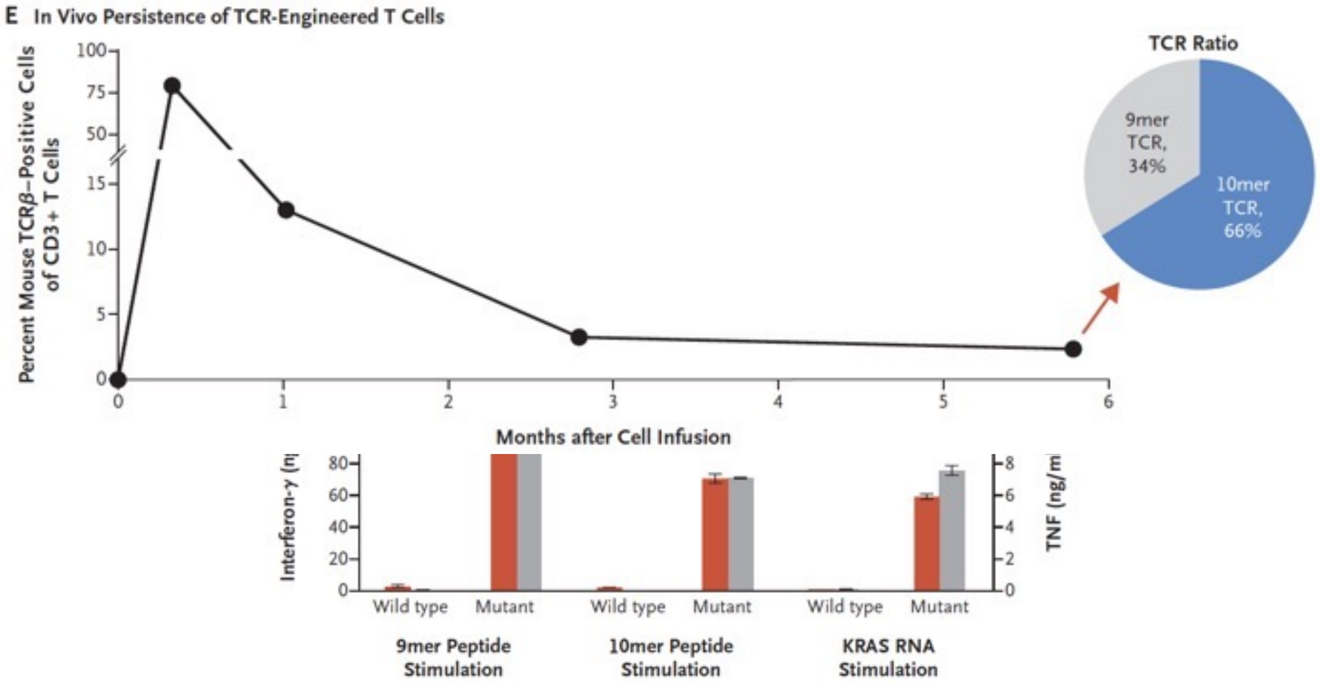
Targeting mutant KRAS with TCR-engineered T cell therapy



BRIEF REPORT

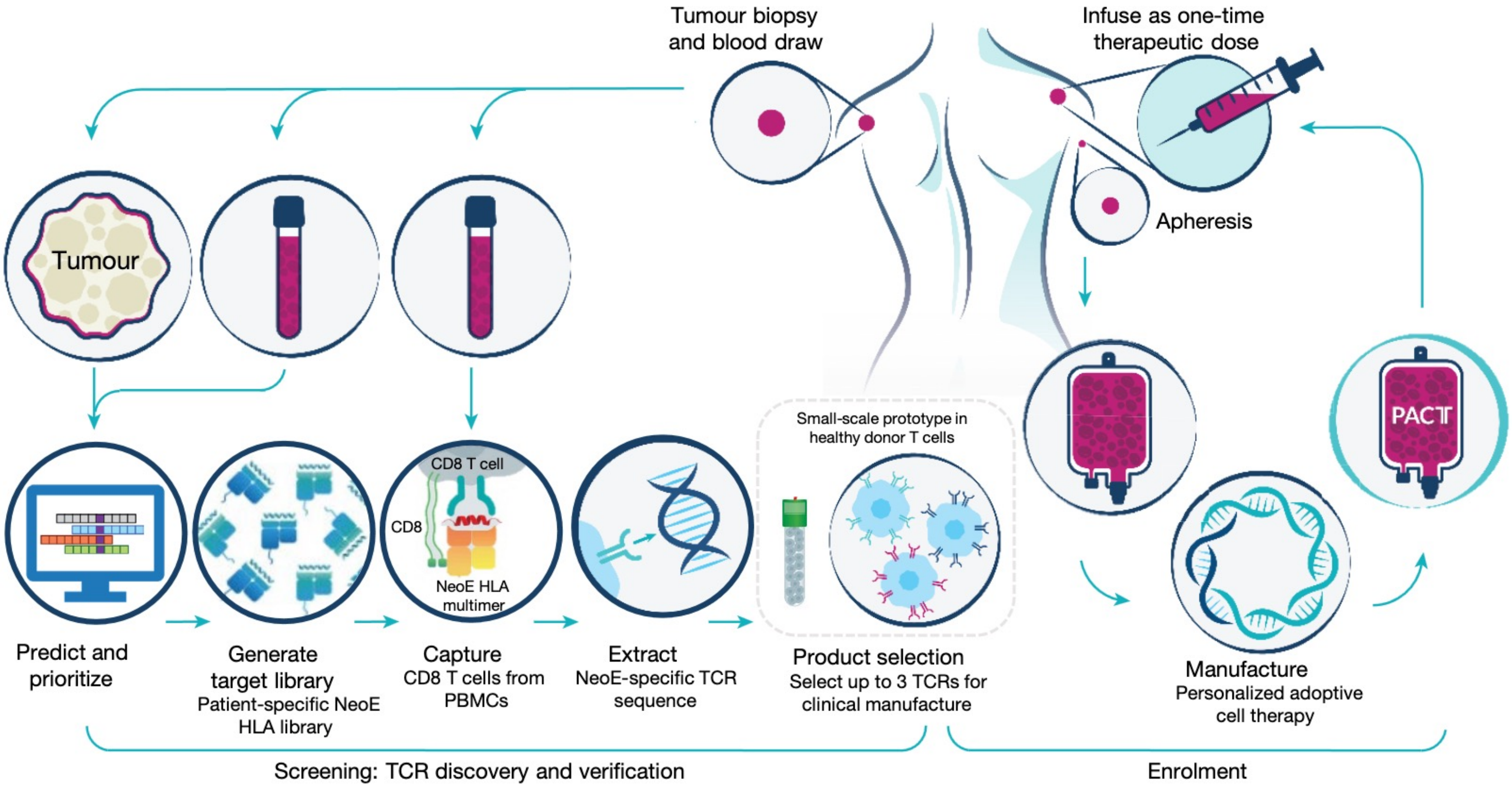
Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.



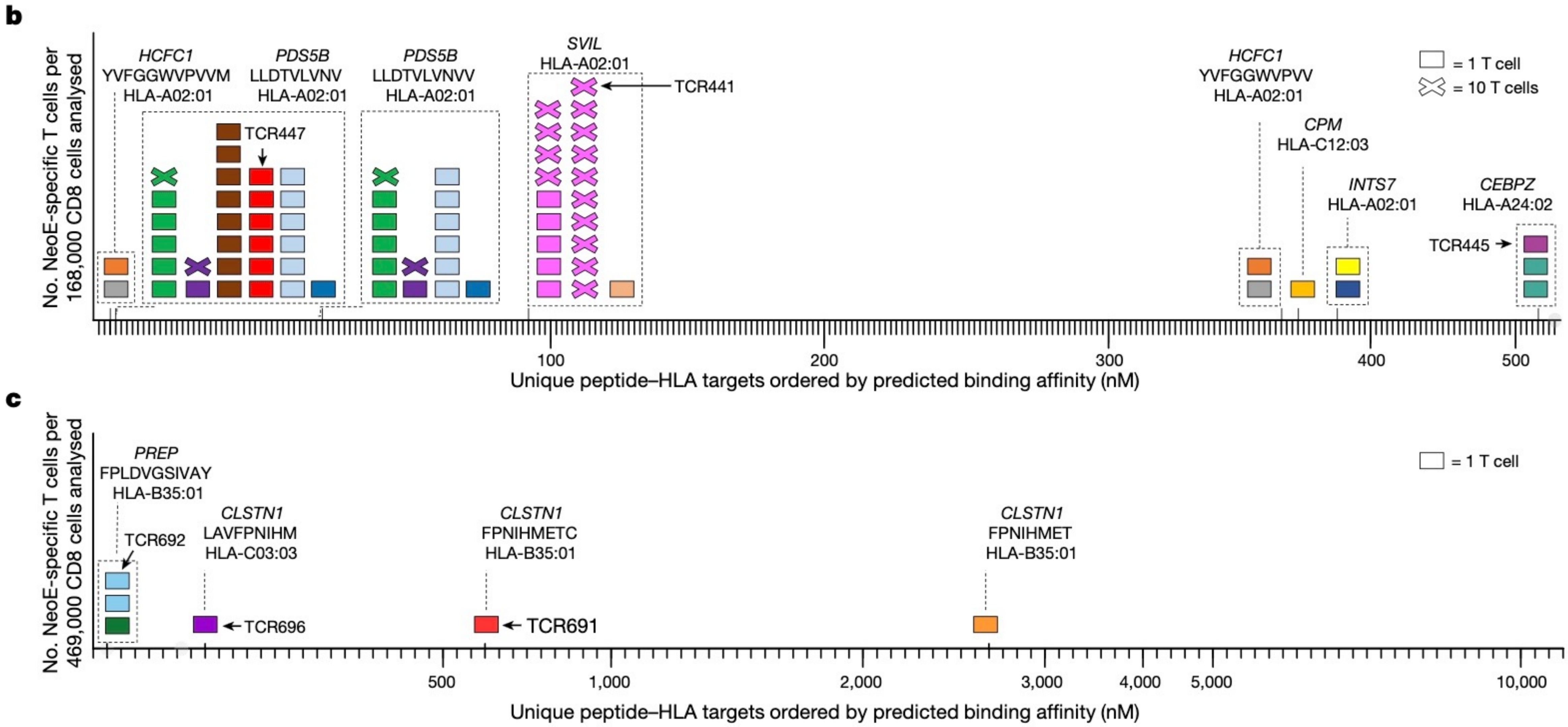
Leidner R et al (2022) *NEJM* 386(22):2112

Personalized TCR-T therapy (PACT Pharma)

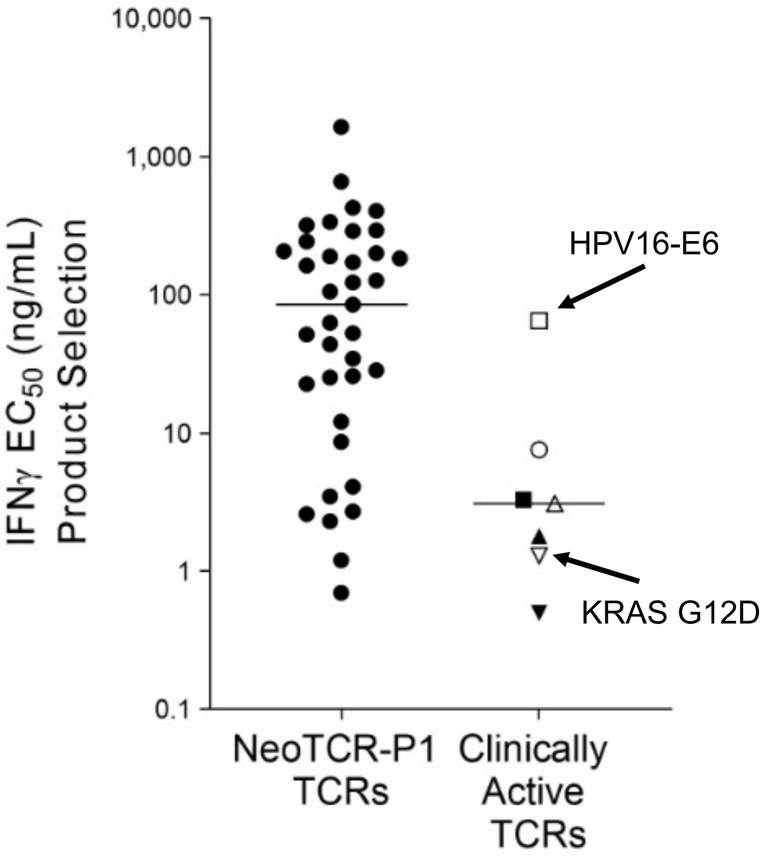


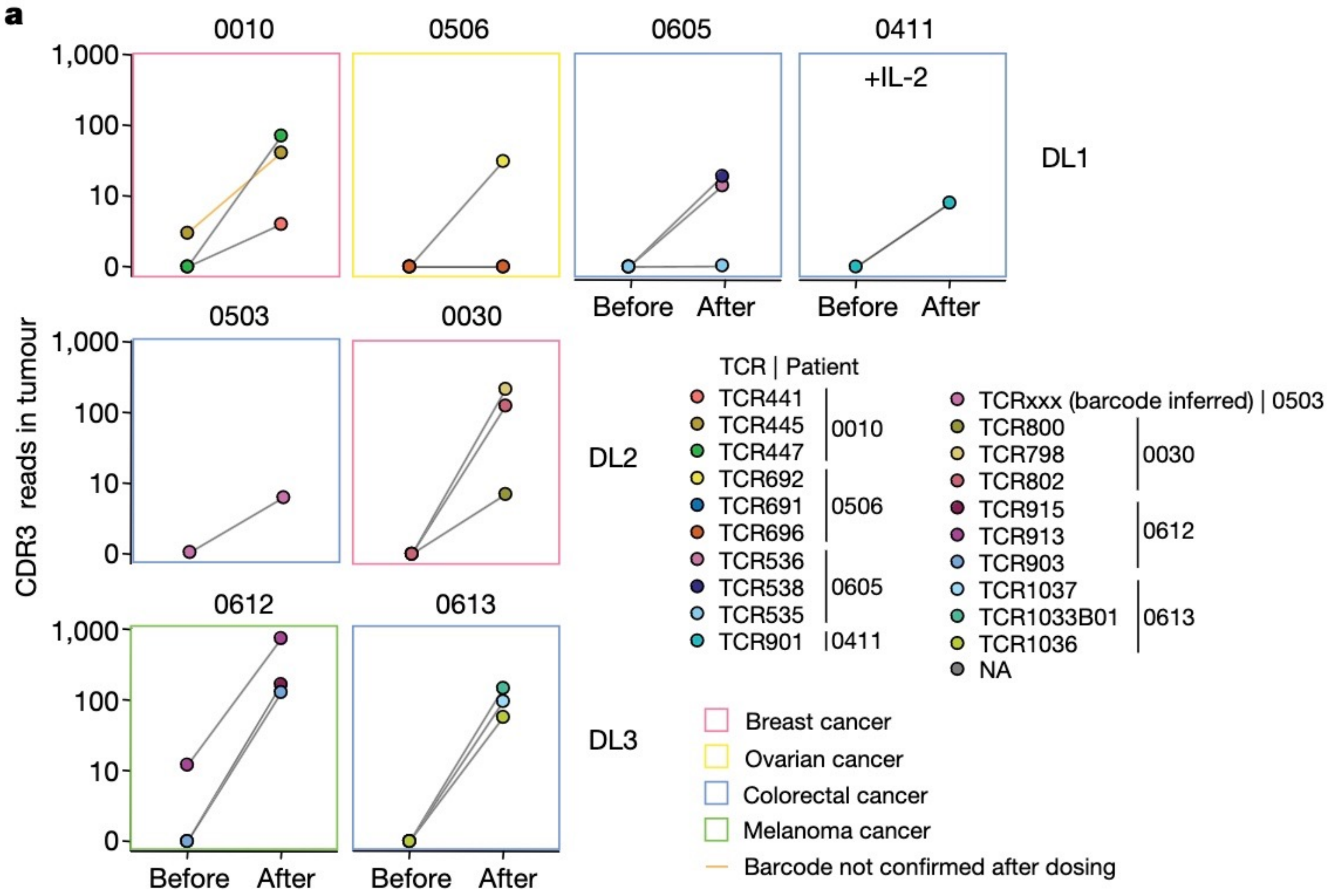
Foy S et al (2023) *Nature* 615:687

Personalized TCR-T therapy (PACT Pharma)



Personalized TCR-T therapy (PACT Pharma)





Personalized TCR-T therapy (PACT Pharma)

Extended Data Table 3 | Patient and disease characteristics, adverse events and response assessment

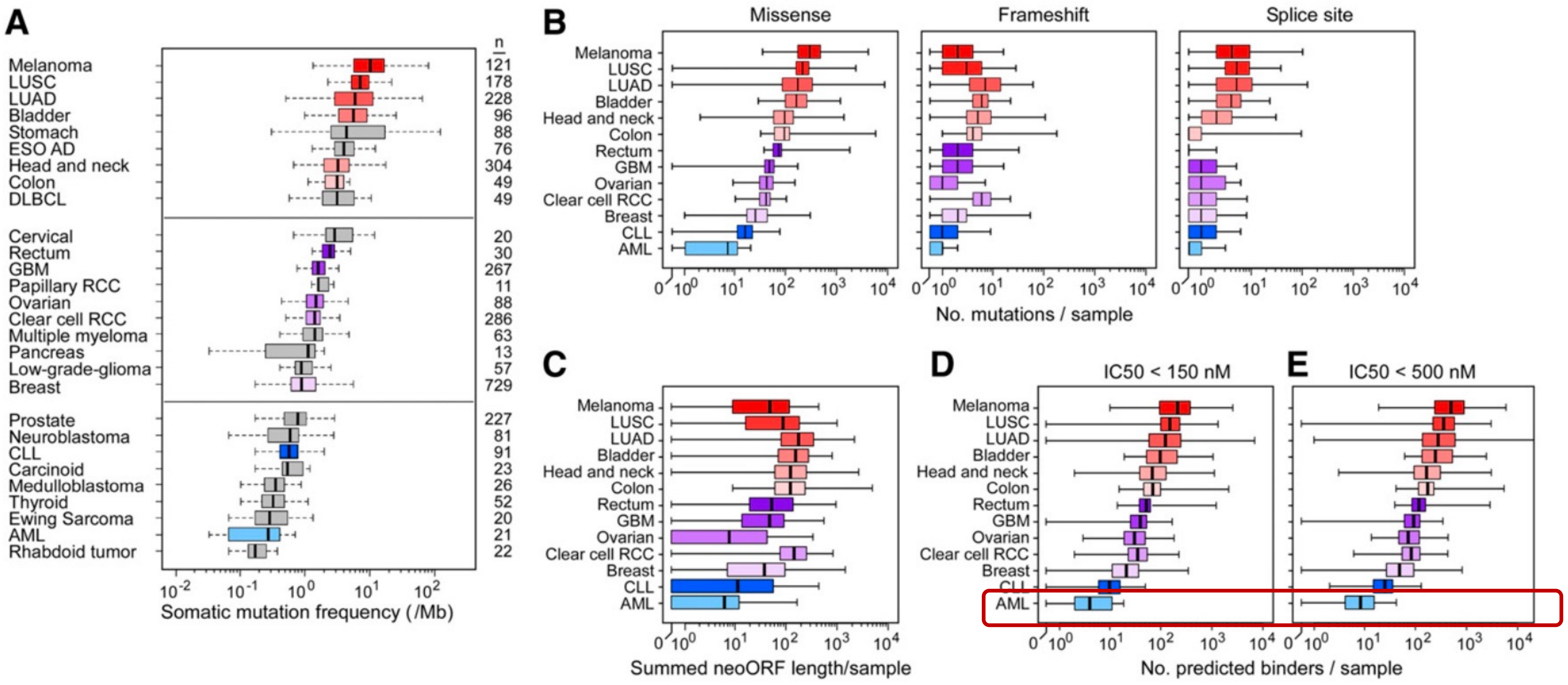
Dose level	Patient ID	Age	Cancer	# Prior regimens	# TCRs	Conditioning regimen	Total NeoTCR+ cell dose	Any AEs ≥ grade 3 and SAEs	TCR-related AEs	Response
DL 1	0010	38	HR+ Breast	7	3	Cy 300 mg/m^2 x3d Flu 30 mg/m^2 x3d	4×10^8	G3 neutropenia		SD (target lesions ↓ 17%) for 4m
	0605	53	MSS-CRC	4	3	Cy 300 mg/m^2 x3d Flu 30 mg/m^2 x3d	4×10^8	SAE D52 small bowel obstruction		PD
	0603	65	MSS-CRC	4	1	Cy 300 mg/m^2 x3d Flu 30 mg/m^2 x3d	2×10^8	COVID-19 + pneumonia		PD
	0506	70	Ovarian	6	3	Cy 300 mg/m^2 x3d Flu 30 mg/m^2 x3d	4×10^8	G3 neutropenia		PD
DL 2	0503	48	MSS-CRC	9	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	1.3×10^9	G4 neutropenia SAE: UTI D74		PD
	0030	45	HR+ Breast	5	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	1.3×10^9	G4 neutropenia		SD at D28 and D56
	0404	47	MSS-CRC	7	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	1.3×10^9	G4 neutropenia SAE G3 Peri-hepatic hematoma		PD
	0611	44	MSS-CRC	5	2	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	9×10^8	G2 Headaches week 2		PD
DL 3	0038	39	MSS-CRC	2	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	4×10^9	G4 neutropenia		PD
	0612	47	Melanoma	3	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	4×10^9	G4 neutropenia		PD
	0613	36	MSS-CRC	3	3	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	4×10^9	SAE: G4 febrile neutropenia	G1 CRS	SD at D28 and D56
	0417	38	MSS-CRC	4	1	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	5.4×10^9	SAE: G4 Hyponatremia SAE: G5 Malignant neoplasm progression		No post-baseline assessment
NeoTCR-P1 + IL-2	0604	40	MSS-CRC	5	2	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	4×10^8 + IL-2	G3 neutropenia and febrile neutropenia; SAE: G3 pancreatitis D40		PD
	0411	58	MSS-CRC	5	1	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	7.5×10^8 + IL-2	G4 neutropenia		SD at D28 and D56
	0026	58	MSS-CRC	5	2	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	1.3×10^9 + IL-2	G4 neutropenia		PD
	1003	68	NSCLC	3	1	Cy 600 mg/m^2 x3d Flu 30 mg/m^2 x4d	1.96×10^9 + IL-2	G3 encephalopathy	G3 encephalopathy	SD at D28

MSS-CRC: Microsatellite Stable Colorectal Cancer; HR: Hormone Receptor; G: Grade; SAE: Serious Adverse Event; CRS: Cytokine Release Syndrome; SD: Stable Disease; PD: Progressive Disease; Y/N: Yes/No.

No clinical responses

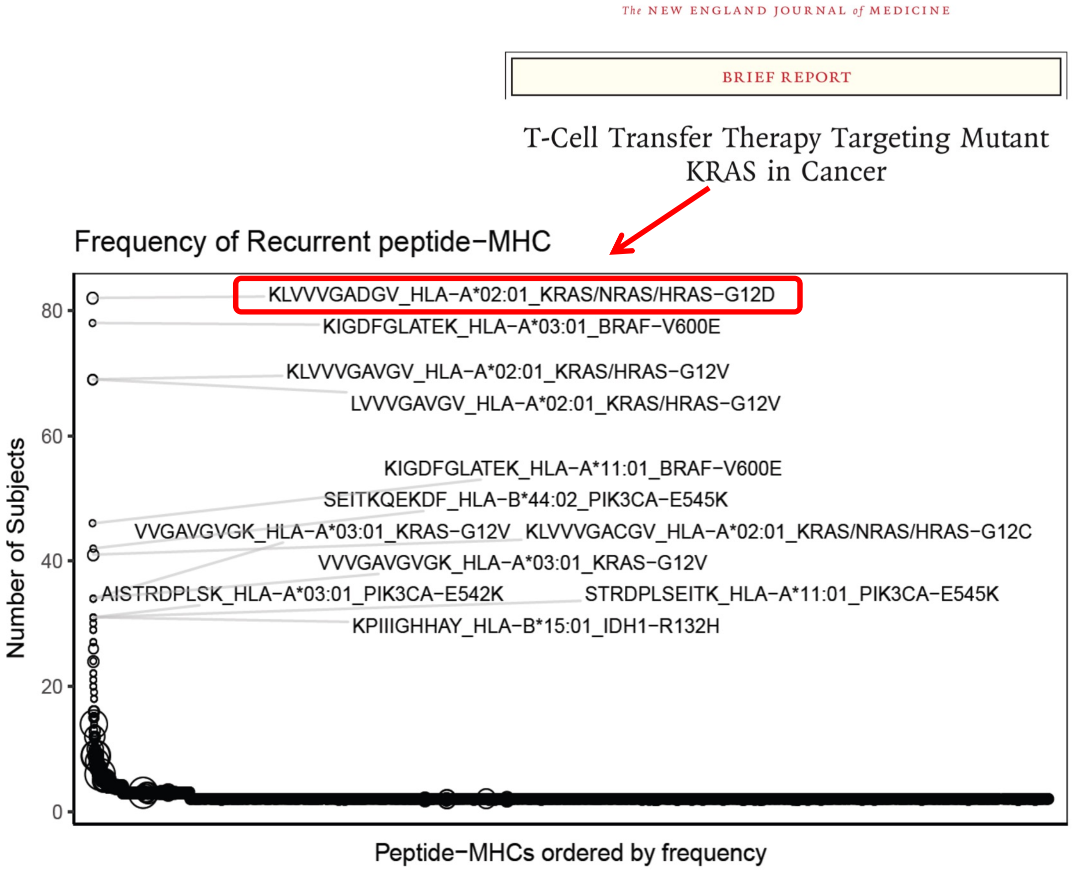
Challenge #1: Not all antigen-specific TCRs are good therapeutics

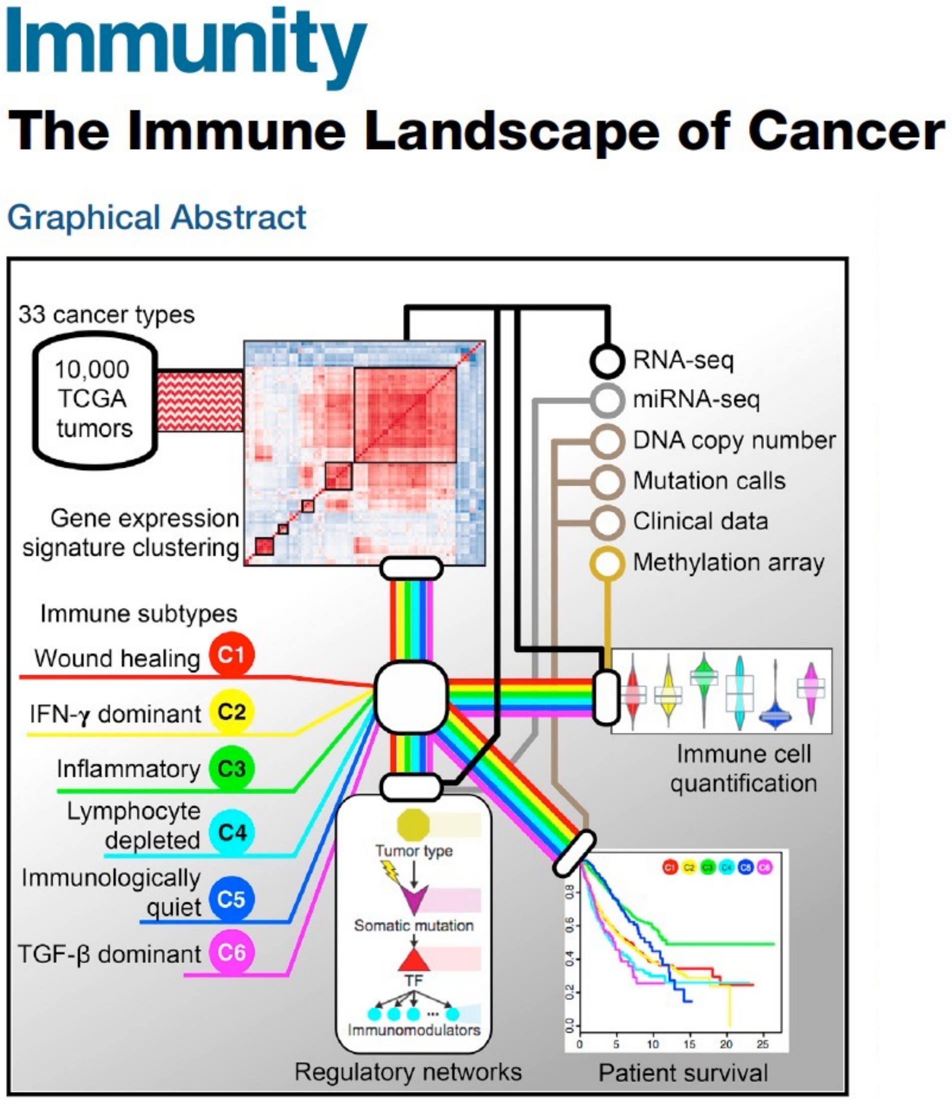
Challenge #2: Some tumors have relatively few neoantigens



Rajasagi. et al. (2014) Blood 124(3):453

Challenge #3: Shared somatic mutation-derived neoantigens are *rare*



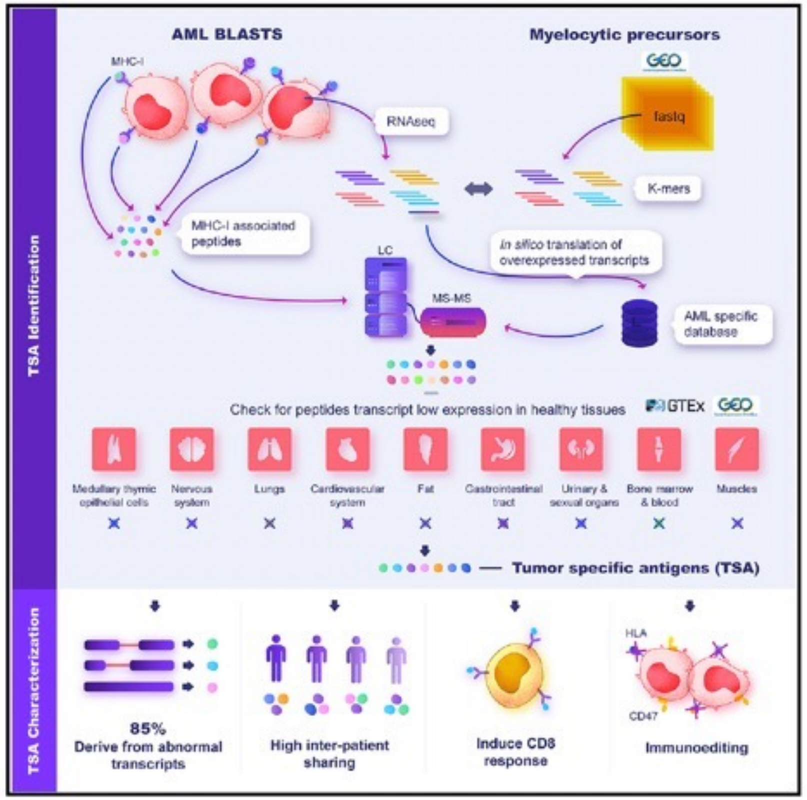


Challenge #4: Most predicted neoantigens are not presented *in vivo*

Immunity

Atypical acute myeloid leukemia-specific transcripts generate shared and immunogenic MHC class-I-associated epitopes

Graphical Abstract



Authors

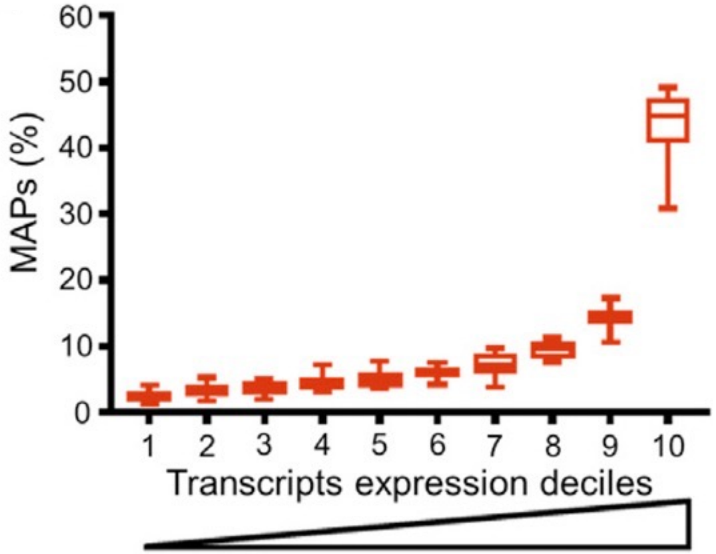
Grégory Ehx, Jean-David Larouche, Chantal Durette, ..., Sébastien Lemieux, Pierre Thibault, Claude Perreault

Correspondence

pierre.thibault@umontreal.ca (P.T.), claude.perreault@umontreal.ca (C.P.)

In brief

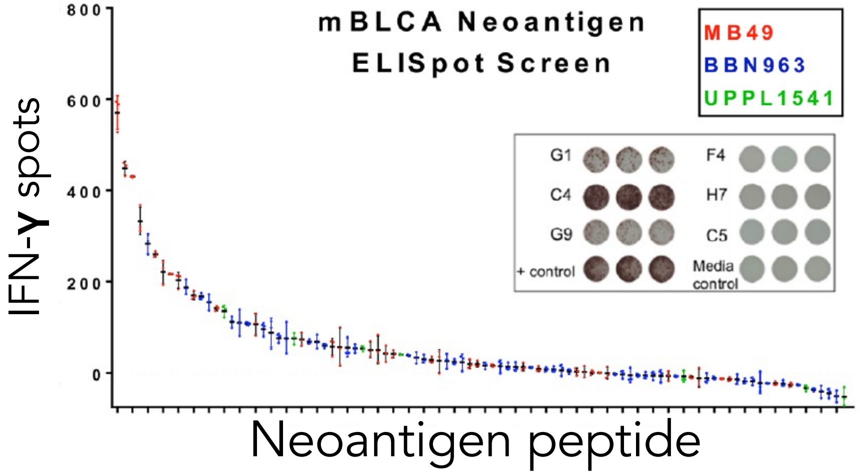
The lack of suitable targets is the main obstacle to immunotherapy of acute myeloid leukemia (AML). Ehx et al. reveal the structure and genomic origin of 58 AML-specific antigens. Epigenetic changes and intron retention are instrumental in the biogenesis of these antigens that represent attractive targets for AML immunotherapy.



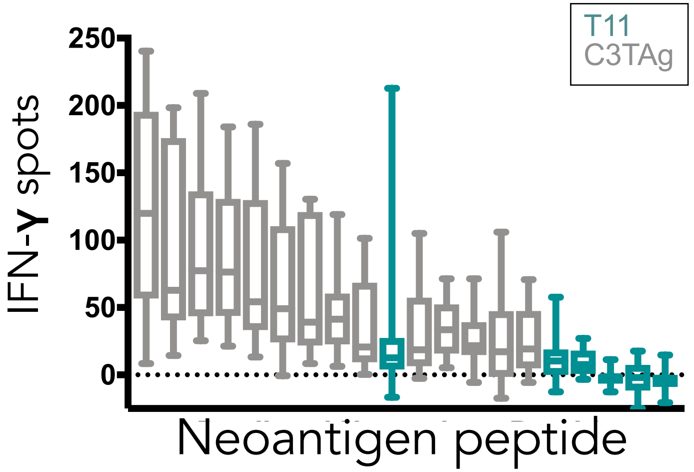
Challenge #5: Most predicted neoantigens are not immunogenic *in vivo*

Christof Smith

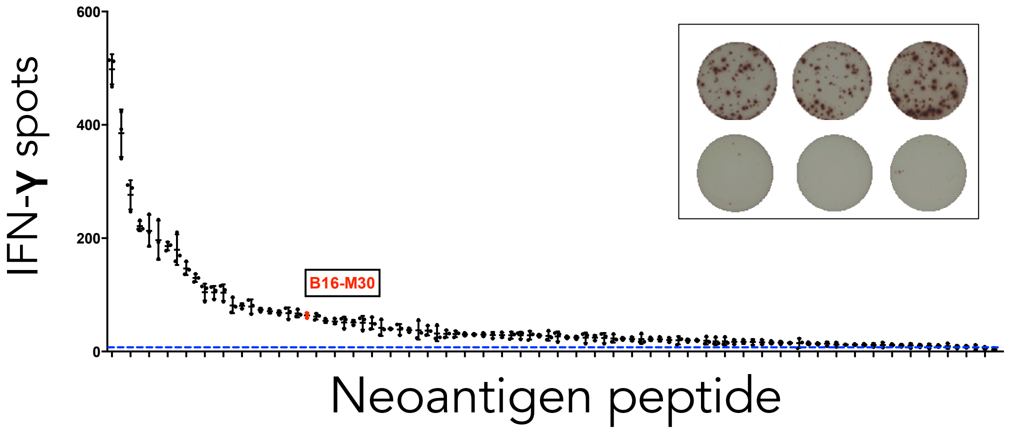
Bladder cancer



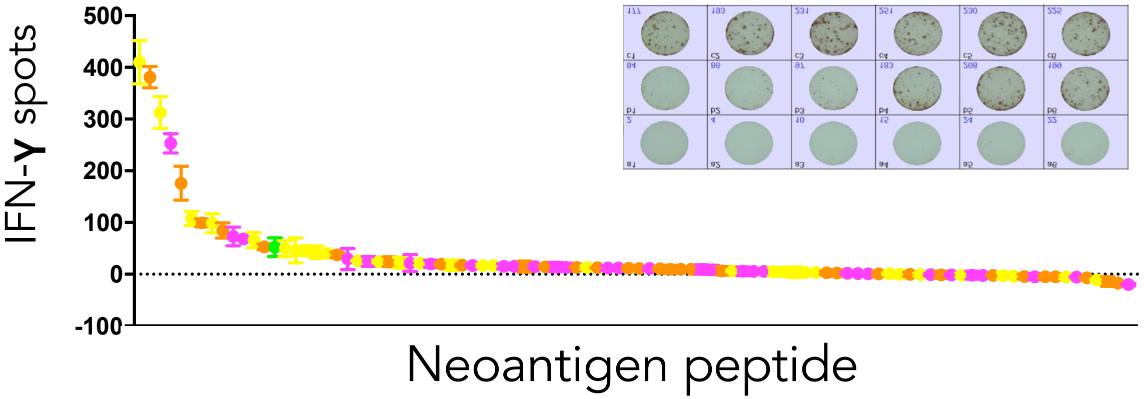
Breast cancer



Melanoma (B16F10)

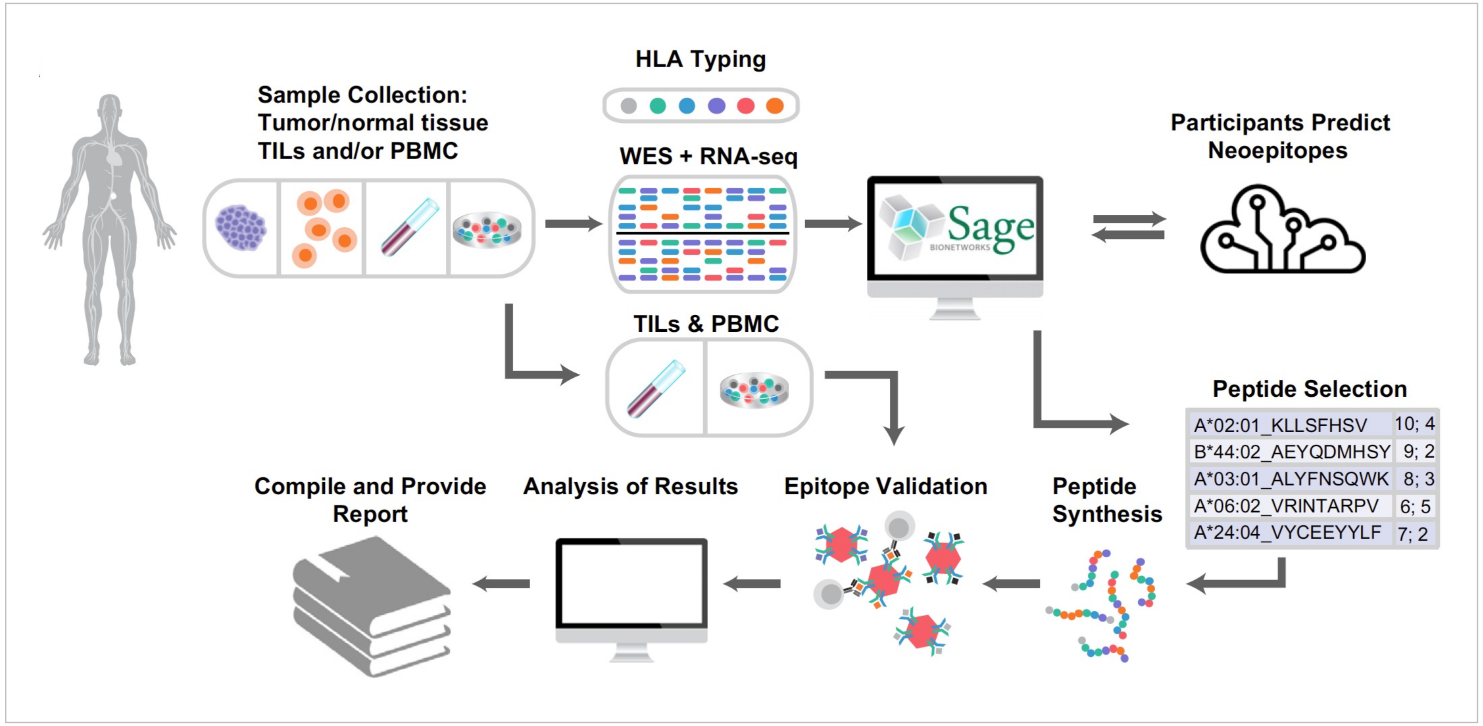


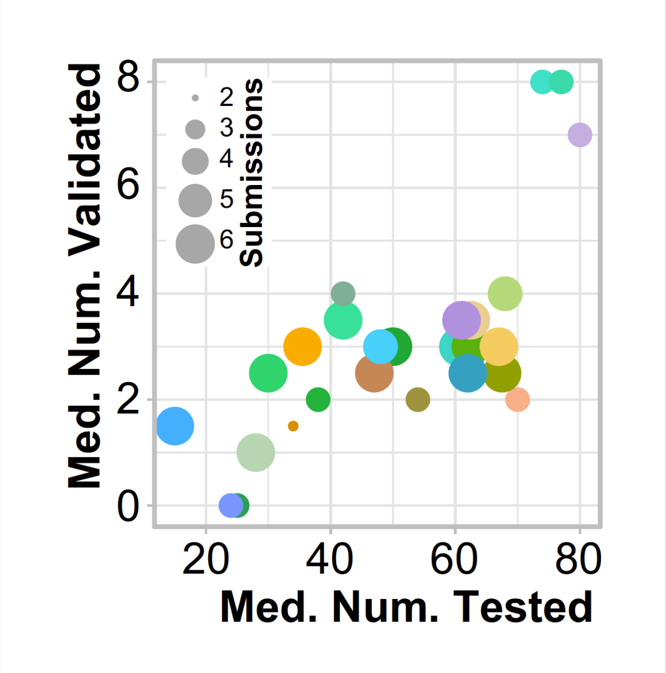
Myeloid leukemia (P815)



Smith C et al. (2019) *Cancer Immunology Research* 10:1591

Challenge #5: Most predicted neoantigens are not immunogenic *in vivo*





- 25 teams
- Submissions ranged from
  7 to 81,904 TSAs per tumor sample.

6% (37) **were immunogenic** among the 608 highly ranked peptides selected and tested for immunogenicity.

Challenge #5: Most predicted neoantigens are not immunogenic *in vivo*

Extended Data Table 1 | Mutational load, predicted neoantigen peptide-HLA capture reagents, recognized mutations and TCR clonotypes for the 16 patients infused in the clinical trial. TMB, tumour mutational burden and was calculated as follows: TMB=#NSM/35 MB, where 35 MB is the length of the sequencing footprint

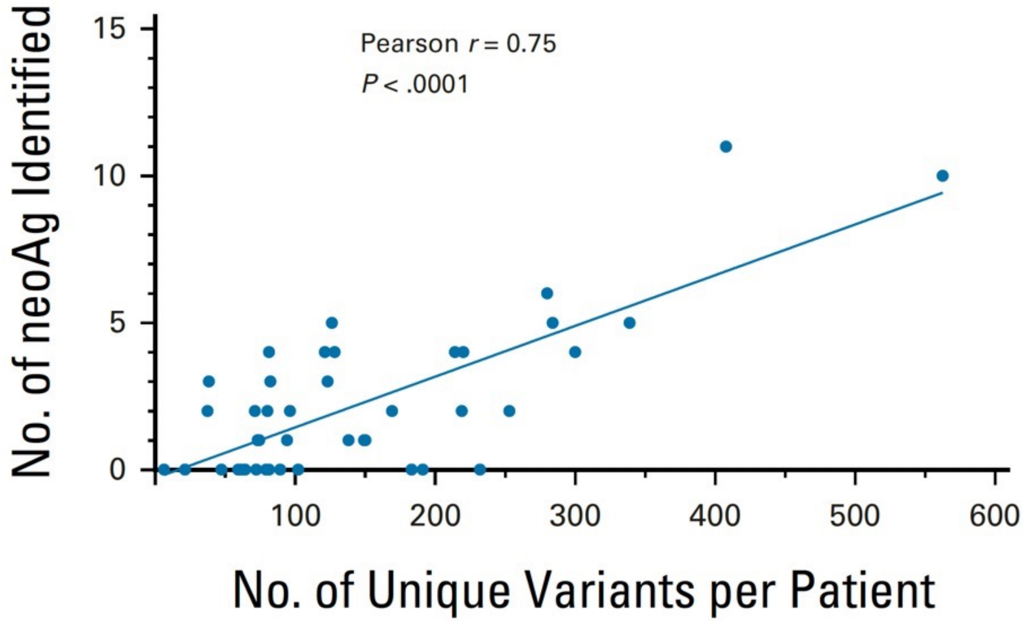
Dose level	Patient ID	# NSM (TMB)	# expressed mutations	HLA alleles covered by HLA library	# HLA-neoantigen capture reagents proposed[*]	# HLA-neoantigen capture reagents produced	# recognized neoantigens[†]	# unique TCRs isolated[‡]	# unique TCRs confirmed[§]
DL 1	0010	468 (13.4)	236	A*02:01, A*24:02, B*35:02, C*12:03	352	262	6	15 (11)	6
	0605	60 (1.7)	23	A*02:01, A*24:02, C*01:01, C*03:03	86	49	4	6	3
	0603	202 (5.8)	88	A*26:01, B*42:01, B*44:02, C*05:01, C*17:01	288	66	3	9 (3)	2
	0506	125 (3.6)	56	A*24:02, B*35:01, B*46:01, C*01:02, C*03:03	352	105	3	5	5
DL 2	0503	88 (2.5)	30	A*24:02, B*39:01, B*52:01, C*07:02, C*12:02	352	130	5	9 (8)	4
	0030	29, 31 (0.9)	20	A*02:01, A*11:01, B*35:01, C*04:01	352	117	7	10 (8)	7
	0404	120 (3.4)	35	A*01:01, A*31:01, B*08:01, B*40:01, C*03:04, C*07:01	352	94	3	7 (6)	6
	0611	74 (2.1)	25	A*01:01, A*24:02, B*57:01, C*04:01, C*06:02	352	67	4	8	4
DL 3	0038	95 (2.7)	34	A*02:01, A*24:02, B*07:02, B*51:01, C*15:02, C*07:02	352	125	10	30 (16)	9
	0612	244 (7.0)	81	A*01:01, B*08:01, B*07:02, C*07:01, C*07:02	352	126	3	16 (14)	3
	0613	43 (1.2)	21	A*02:01, C*07:02	352	83	5	8	6
	0417	107 (3.1)	62	A*02:01, A*25:01, B*15:01, B*18:01, C*03:03, C*12:03	352	147	11	17 (10)	6
NeoTCR-P1 + IL-2	0604	102 (2.9)	30	A*01:01, A*11:01, B*08:01, B*35:01, C*04:01, C*07:01	352	98	3	3	2
	0411	83 (2.4)	32	A*01:01, A*02:01, B*07:02, B*57:01, C*06:02, C*07:02	352	87	5	5	3
	0026	89 (2.5)	48	A*01:01, B*08:01, C*07:01	352	35,104	6	22 (11)	4
	1003	172 (4.9)	94	A*02:01, A*26:01, B*15:01, B*35:01, C*03:04, C*04:01	352	146	5	5	3
Median		102 (2.9)	35	5	352	104	5	8	4
Total				34 (unique)	5302	1841	83	175 (127)	73

[*]A maximum of 352 predicted neoantigen capture reagents were provided for protein synthesis.
[†]Number of unique non-synonymous somatic mutations recognized by one or more TCRs isolated from patient PBMCs.
[‡]Number of unique TCRs isolated from the patient PBMCs, number in parenthesis indicates the numbers that were passed on for confirmation, if it was less than the total number of unique TCRs isolated.
[§]Number of unique TCRs that were transfected into healthy donor cells and showed specific binding to the matched peptide-HLA and IFNγ secretion with peptide-HLA stimulation.
drome; SD: Stable Disease; PD: Progressive Disease; Y/N: Yes/No.

original reports

Breast Cancers Are Immunogenic: Immunologic Analyses and a Phase II Pilot Clinical Trial Using Mutation-Reactive Autologous Lymphocytes

Nikolaos Zacharakis, PhD[1]; Lutfi M. Huq, BA[1]; Samantha J. Seitter, DO[1]; Sanghyun P. Kim, PhD[1]; Jared J. Gartner, MSc[1]; Sivasish Sindiri, MSc[1]; Victoria K. Hill, PhD[1]; Yong F. Li, BS[1]; Biman C. Paria, PhD[1]; Satyajit Ray, PhD[1]; Billel Gasmi, MD[2]; Chyi-chia Lee, MD, PhD[2]; Todd D. Prickett, PhD[1]; Maria R. Parkhurst, PhD[1]; Paul F. Robbins, PhD[1]; Michelle M. Langhan, BS[1]; Thomas E. Shelton, BS[1]; Anup Y. Parikh, MD[1]; Shoshana T. Levi, MD[1]; Jonathan M. Hernandez, MD[3]; Chuong D. Hoang, MD[4]; Richard M. Sherry, MD[1,5]; James C. Yang, MD[1]; Steven A. Feldman, PhD[1,6]; Stephanie L. Goff, MD[1]; and Steven A. Rosenberg, MD, PhD[1]



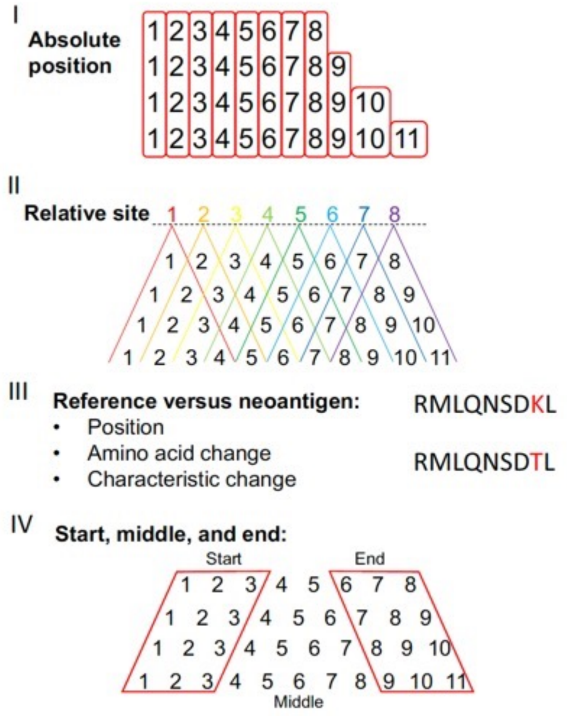
Improving neoantigen immunogenicity prediction

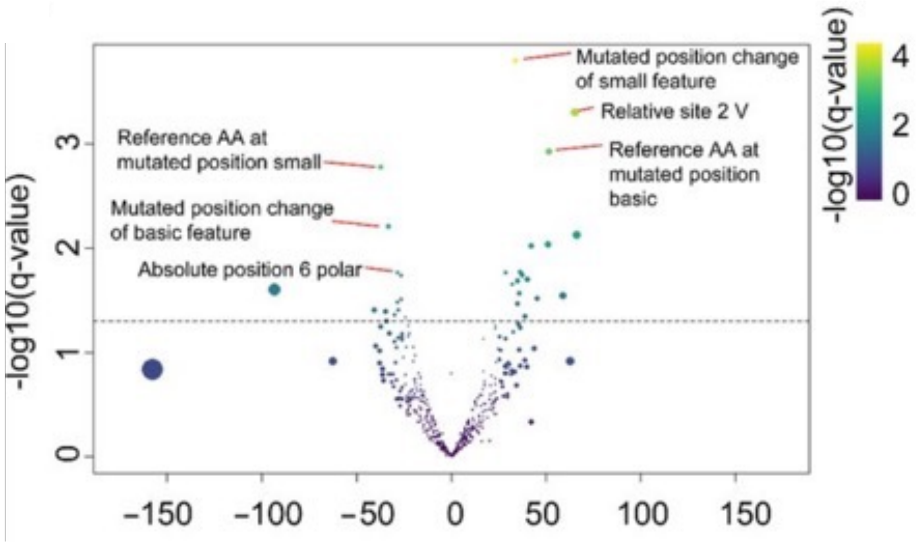
Christof Smith

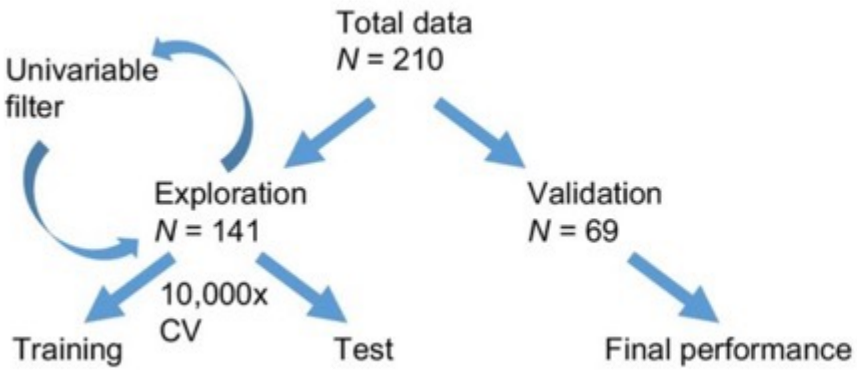
A

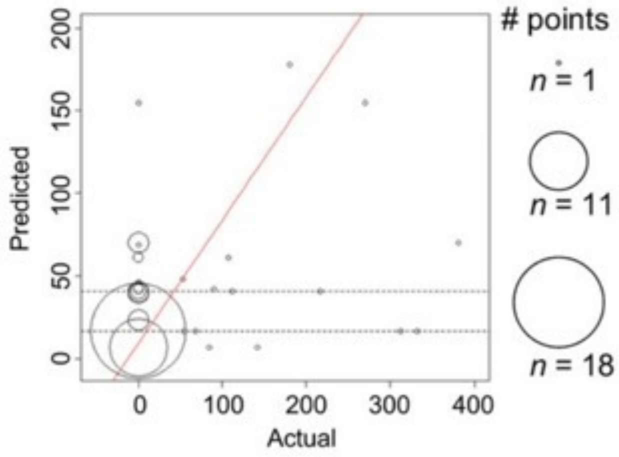
Model	Haplotype	Class I	Class II
B16F10	b	37	36
BBN963	b	34	18
MB49	b	29	8
UPPL1541	b	2	5
P815	d	96	N/A
T11	d	12	1

C

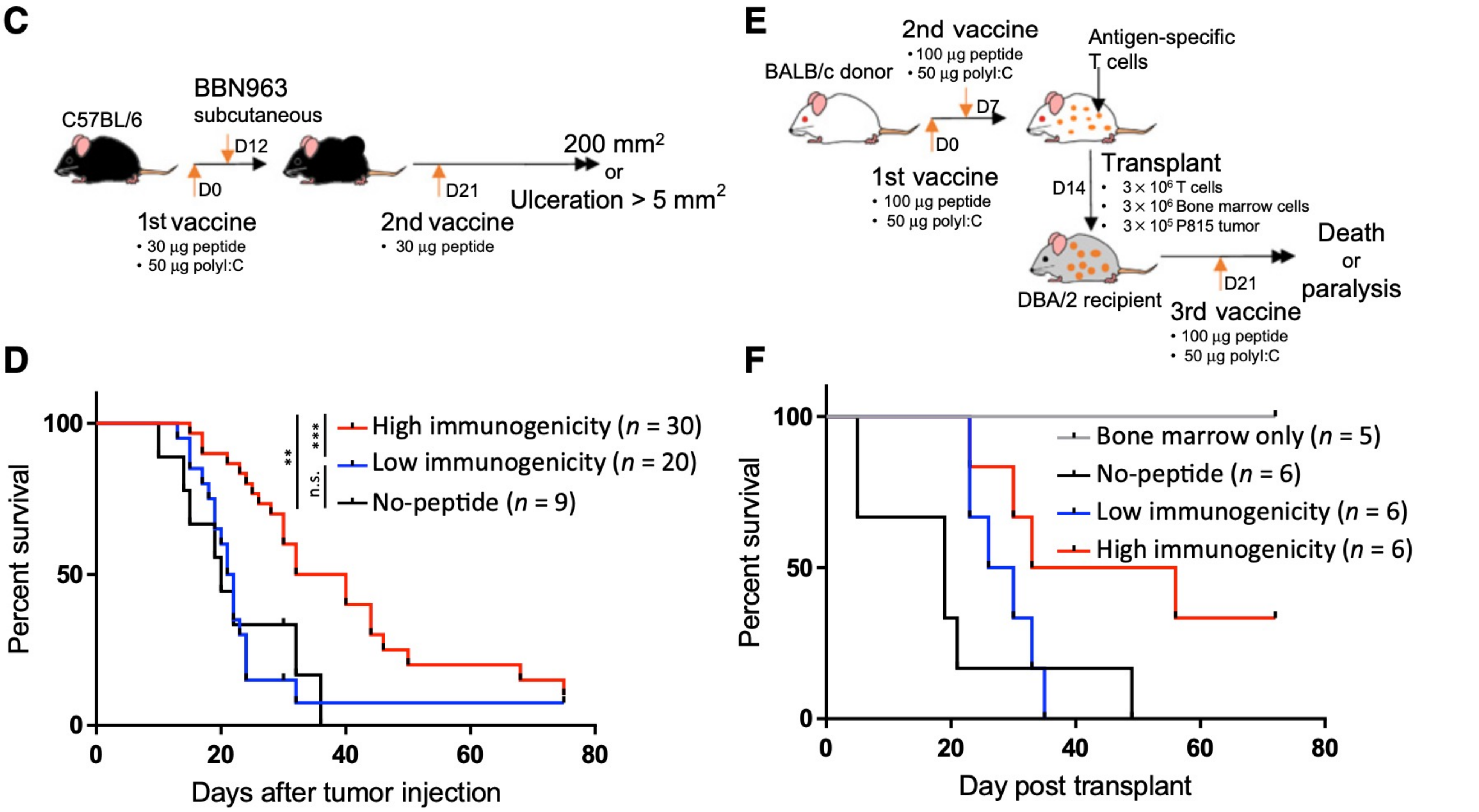




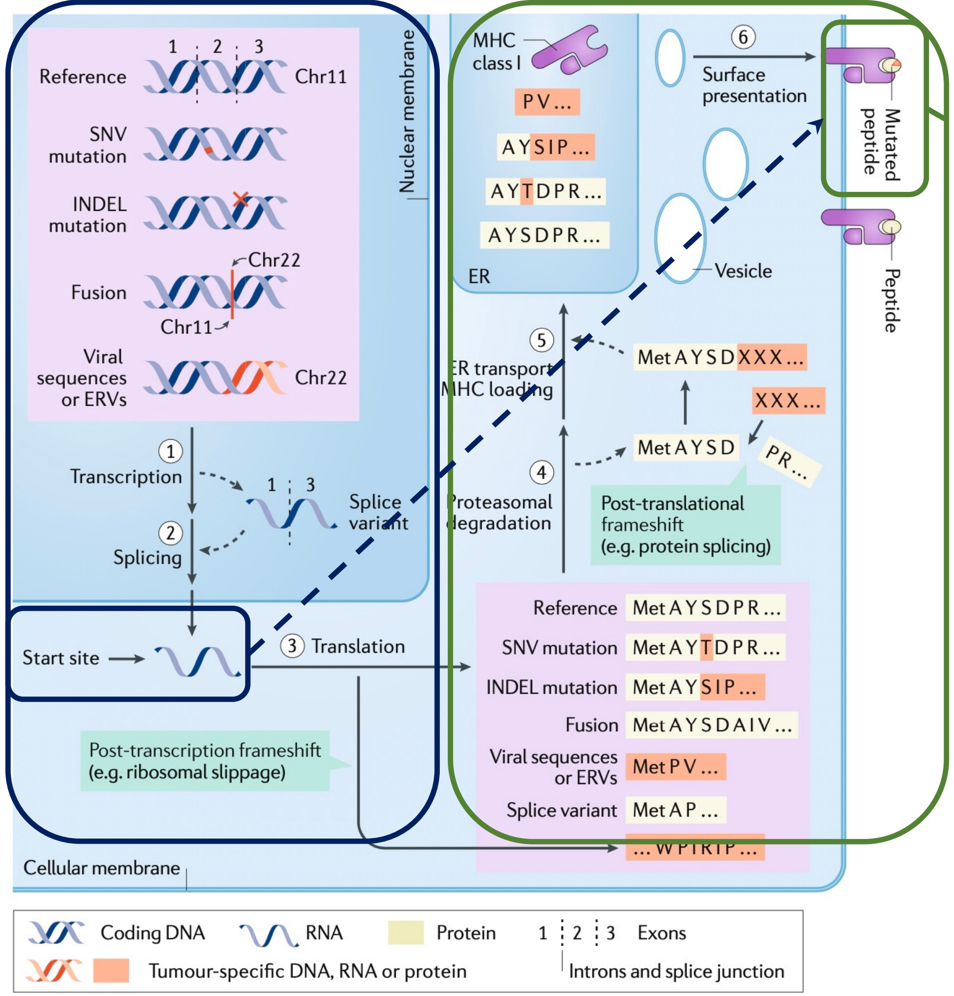


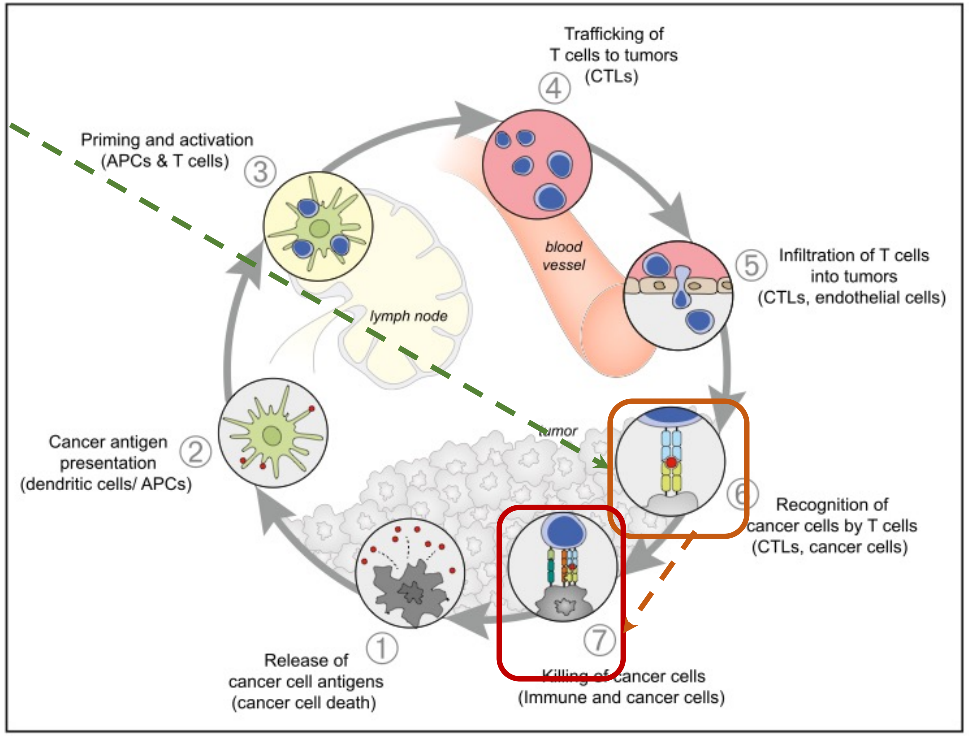


Improving neoantigen immunogenicity prediction



Smith C et al. (2019) *Cancer Immunology Research* 10:1591





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- Confirm with any T cell quantitation &/or functional assay
- Understand mechanisms of antigen-specific T cell generation

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1. Identify neoantigen coding sequence variants

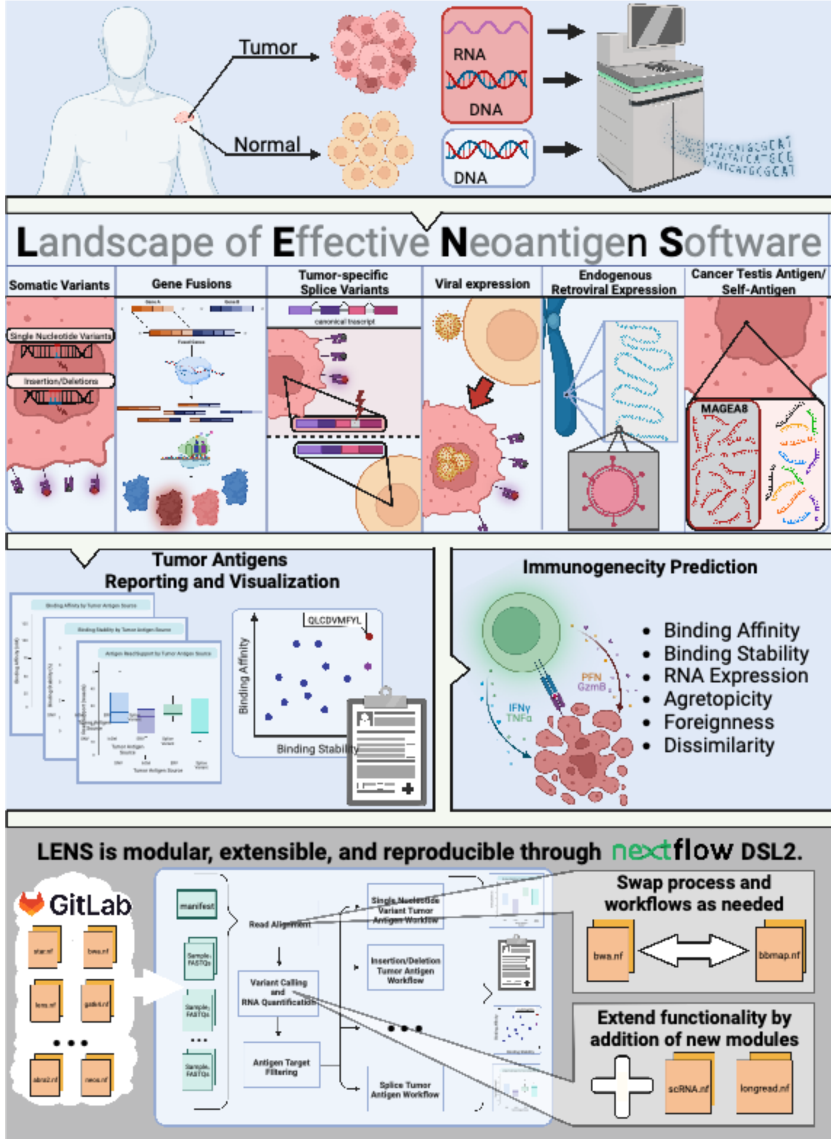
2. Predict MHC-binding neoantigen peptides

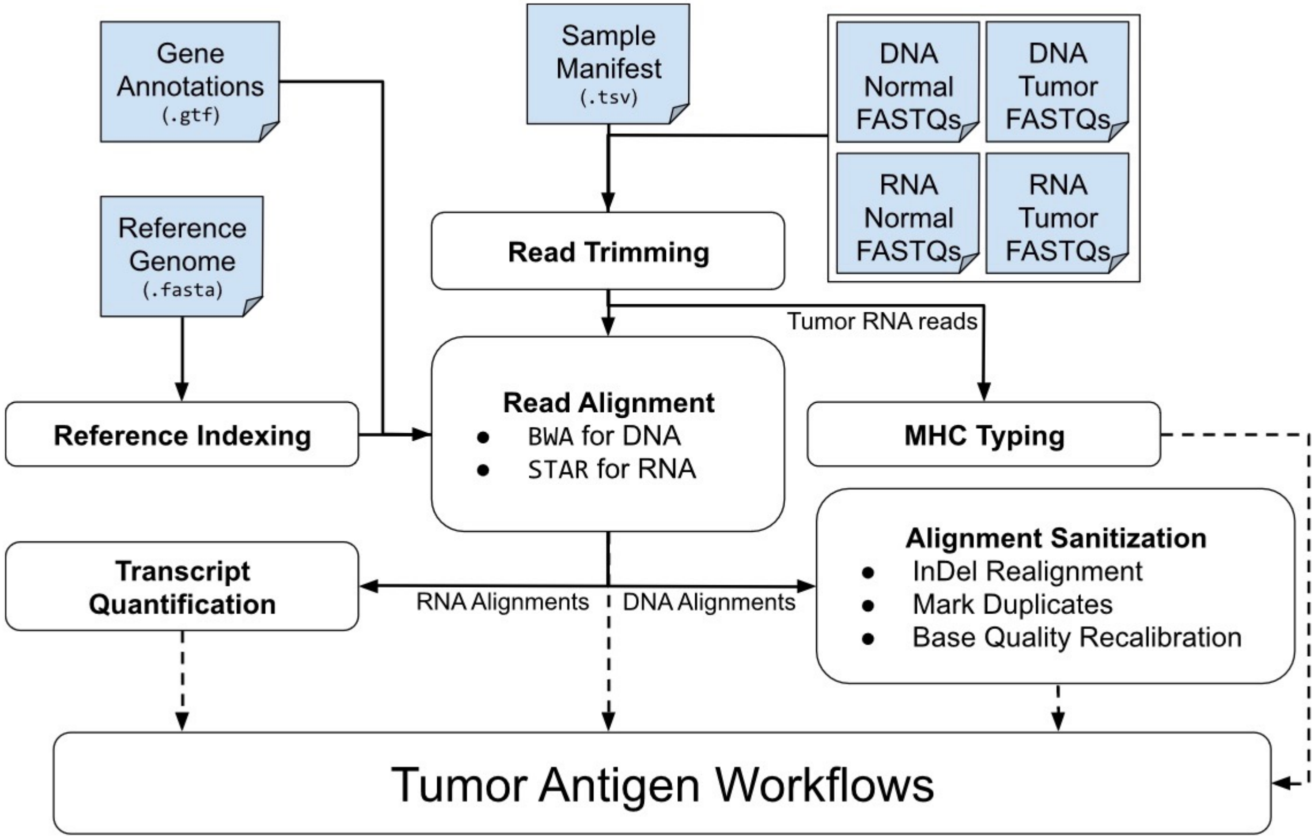
- Confirm with mass spectrometry / immunopeptidomics
- Understand mechanisms of peptide selection

Smith C. et al. (2019) *Nature Reviews* Cancer; Chen & Mellman (2013) *Immunity* 39:1

Landscape of Effective Neoantigen Software (LENS)

Steven Vensko





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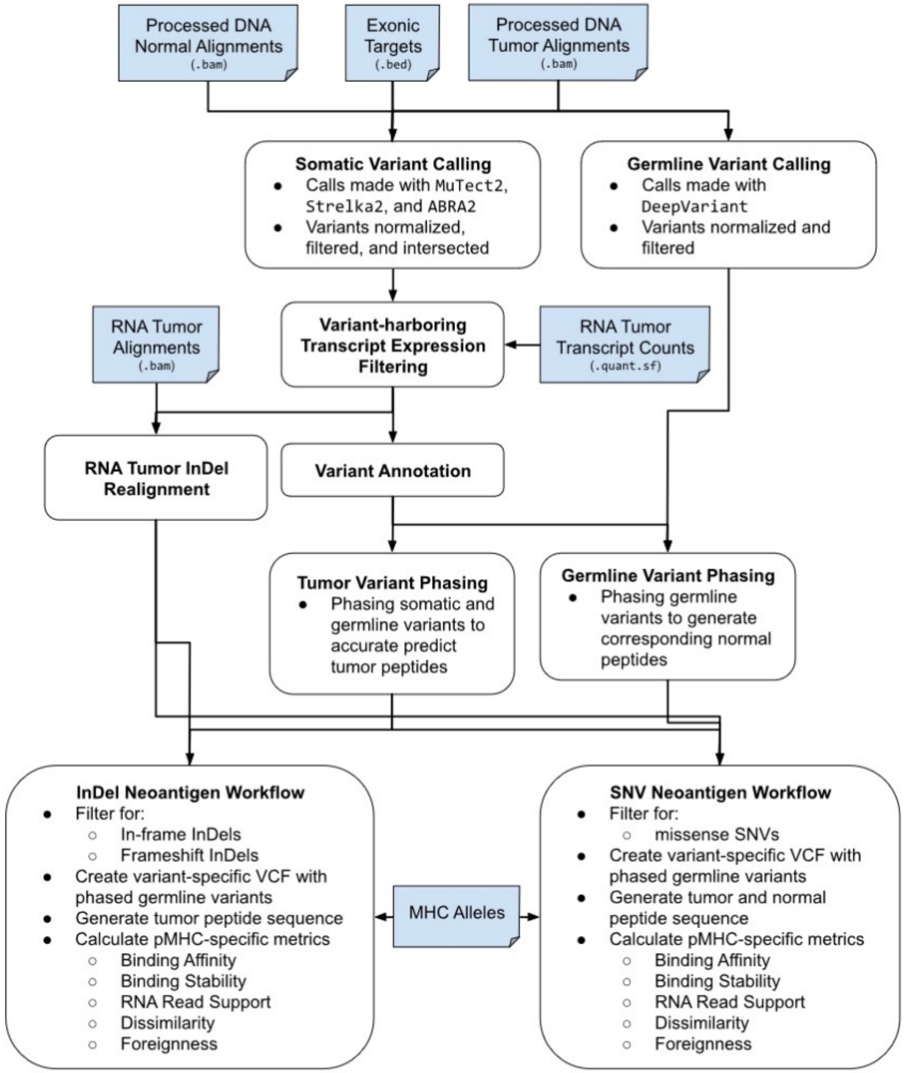
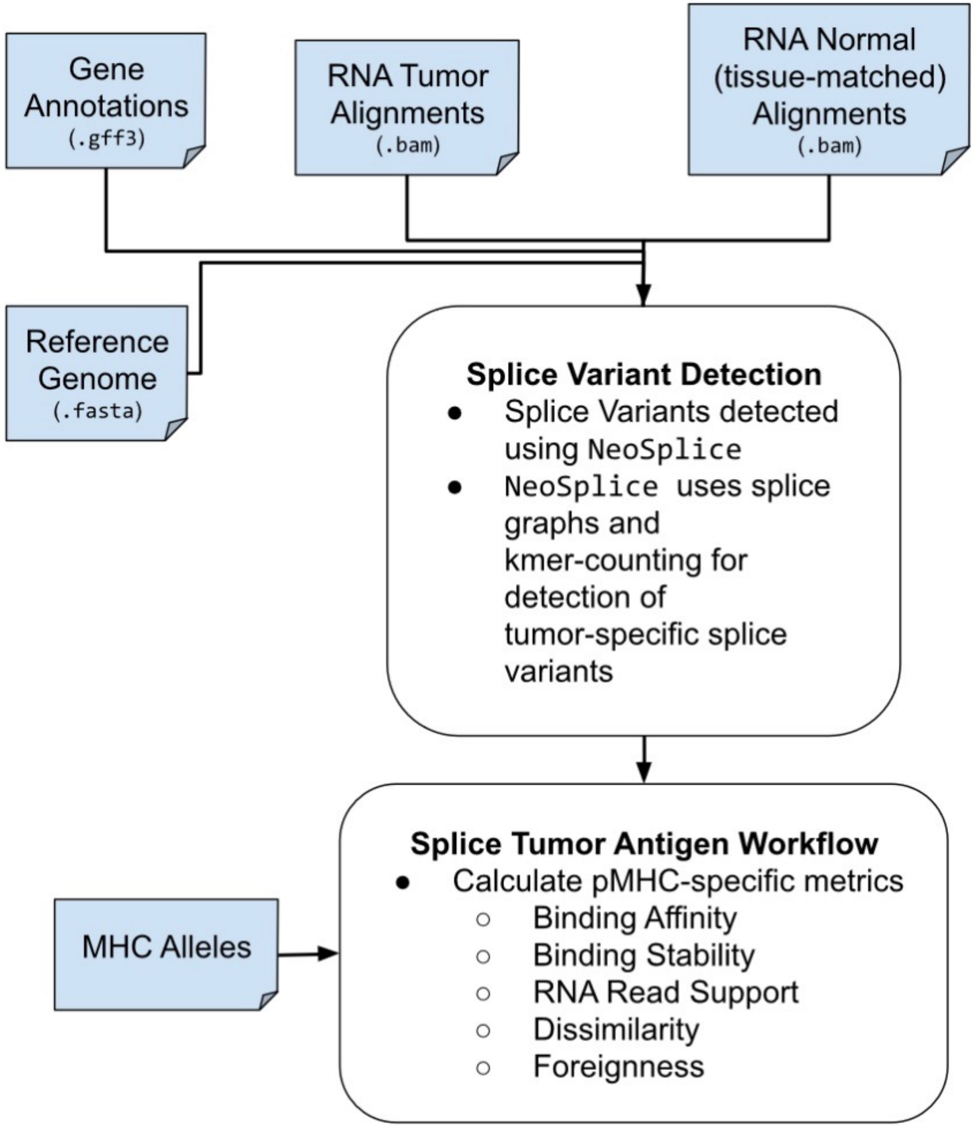
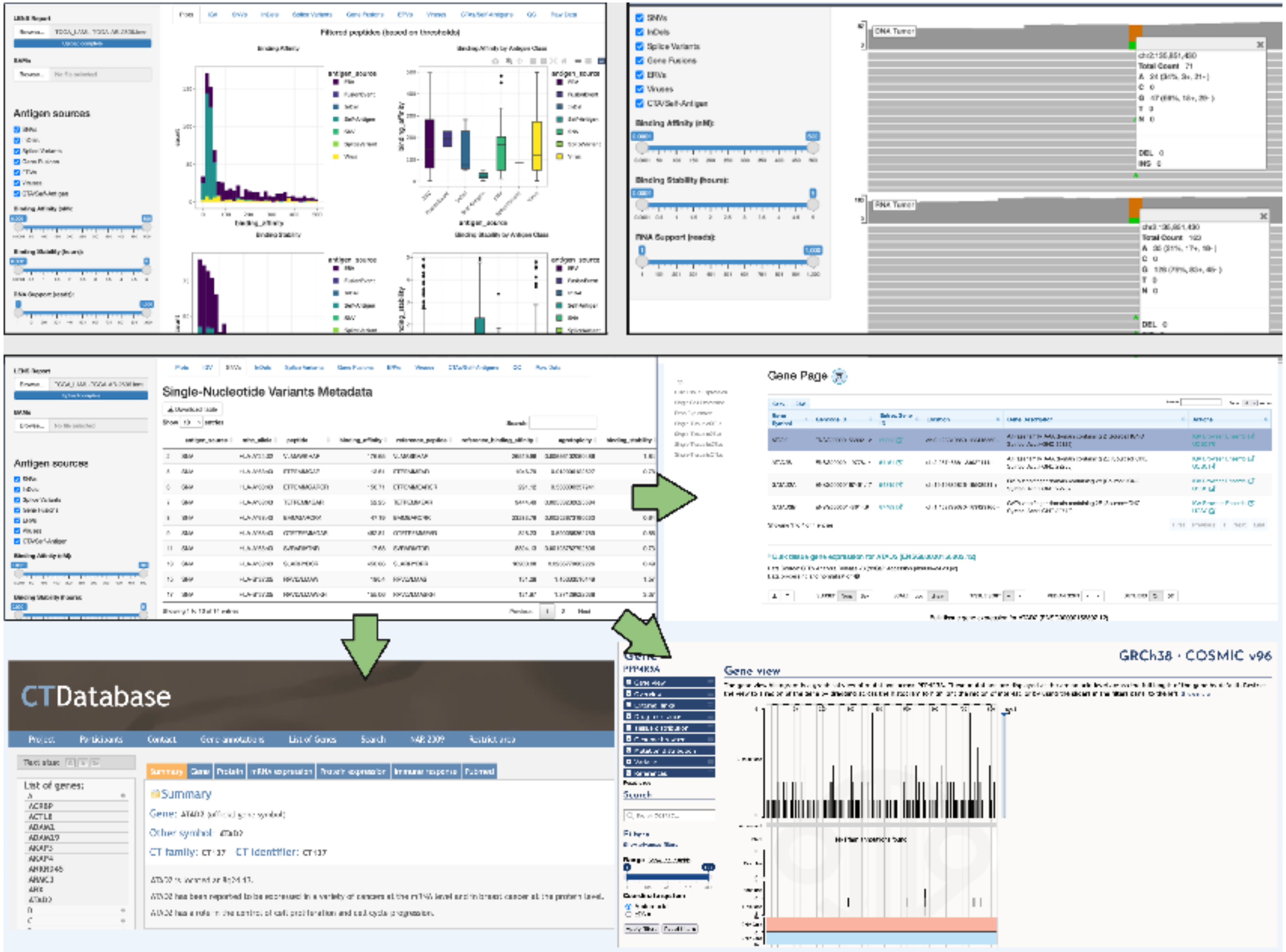


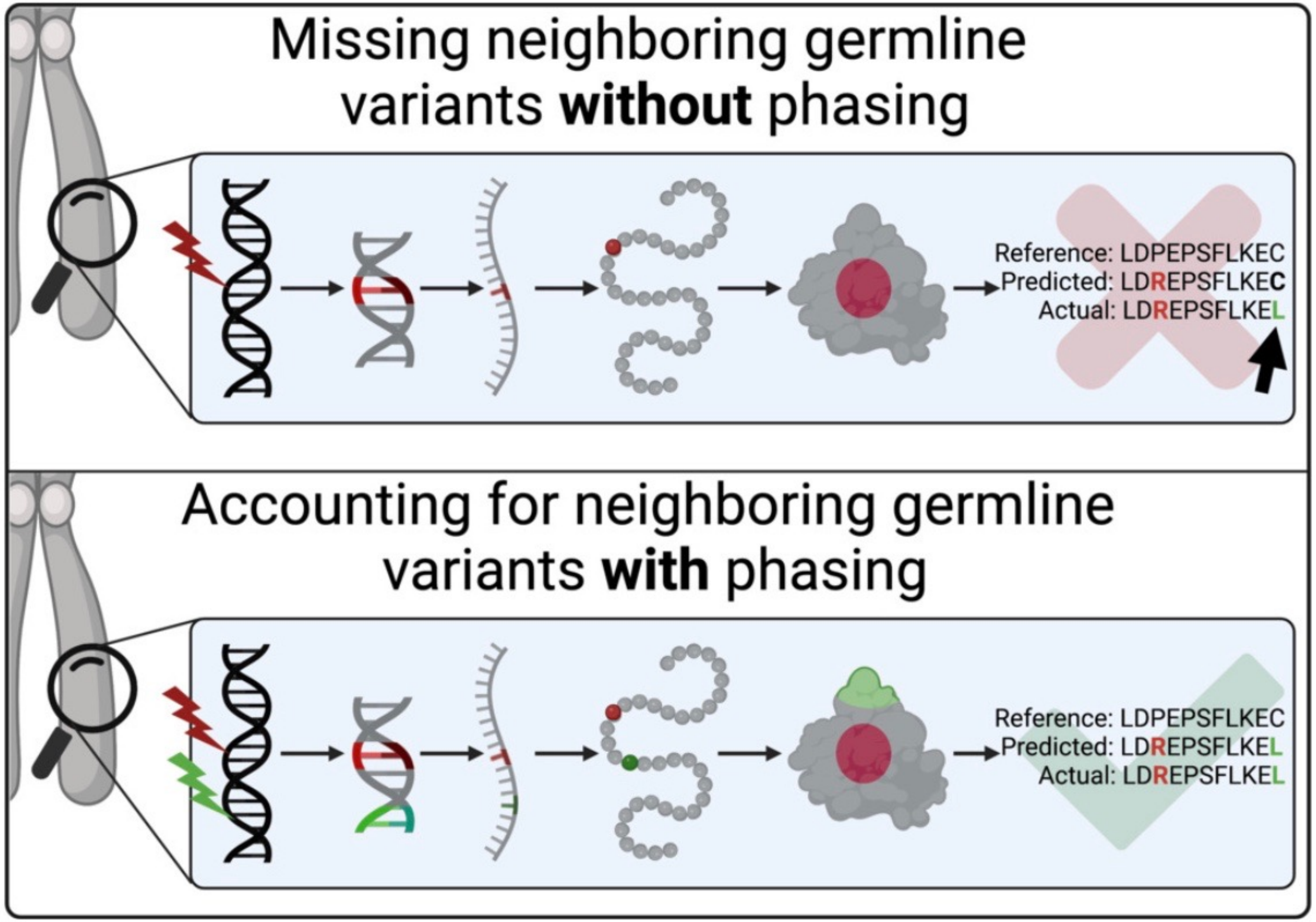


Vensko et al. (2023) *Bioinformatics* 39(6):btad322



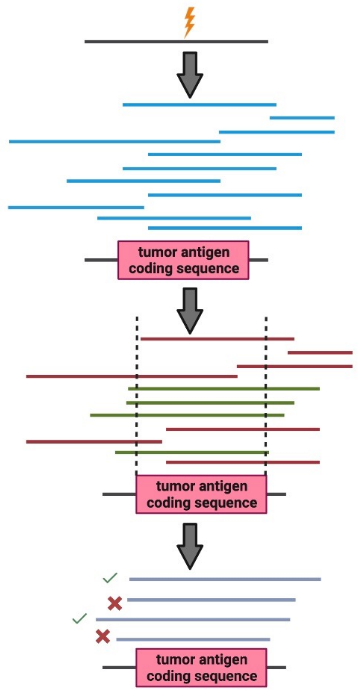
Antigen sources
Filtered peptides (based on thresholds)
Binding Affinity
Binding Affinity (nM):
Binding Stability (hours):
RNA Support (reads):
DNA Tumor
RNA Tumor
Single-Nucleotide Variants Metadata
Gene Page
CTDatabase
Project
Participants
Contact
List of Genes
Search
Summary
Gene view
GRCh38 · COSMIC v96

Phasing of multiple variants including germline variants



Harmonized antigen coding transcript expression quantification

SNV & InDel



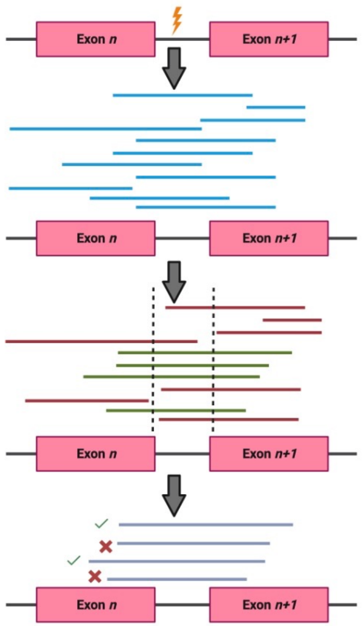
Somatic variant detected in DNA

Fetch all reads covering region of interest from RNA tumor BAM

Filter to reads that are able to contain the entire peptide coding sequence

Count reads that contain variant peptide coding sequence

Splice Variant



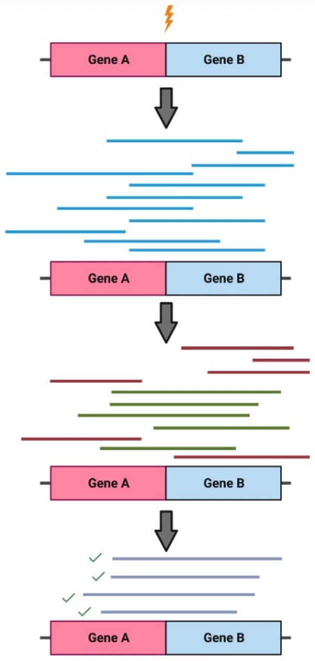
Splice variant detected in RNA

Fetch all reads covering region of interest from RNA tumor BAM

Filter to reads that are able to contain the entire peptide coding sequence

Count reads that contain splice peptide coding sequence

Gene Fusion



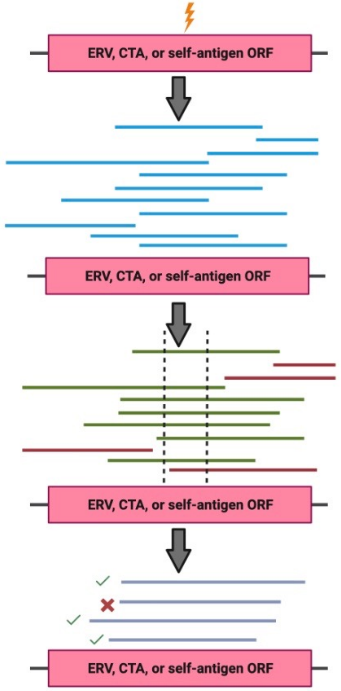
Gene fusion detected in RNA

Fetch all reads covering region of interest from RNA tumor BAM

Filter to reads that cover fusion junction (shown) or map discordantly.

Count reads that contain fusion peptide coding sequence

Virus, ERV & CTA



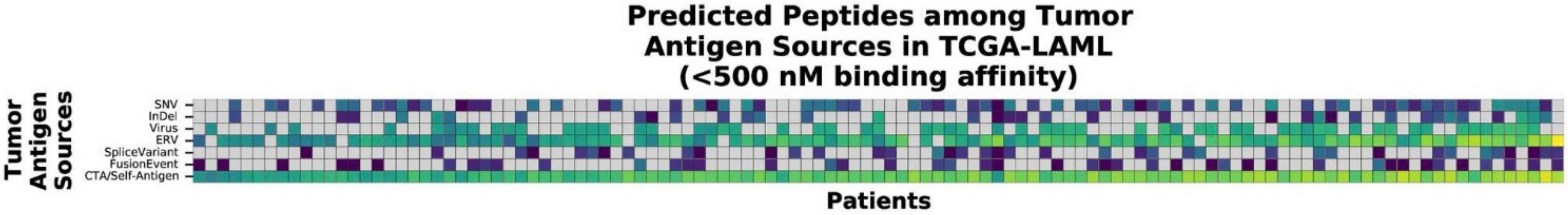
ERV, CTA, or self-antigen predicted targetable peptide discovered in RNA

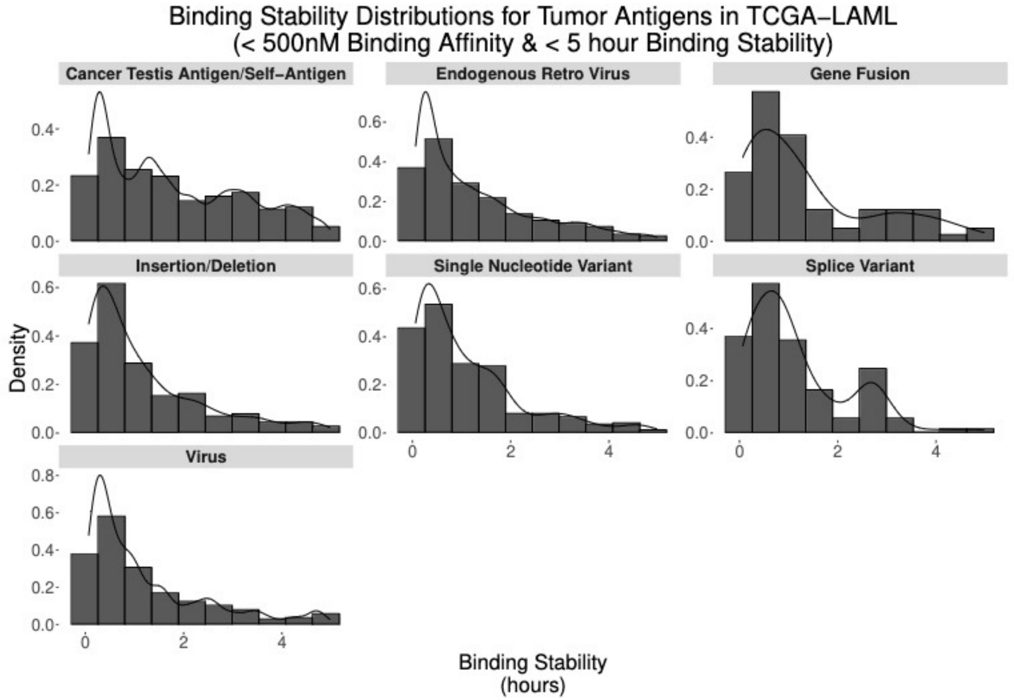
Fetch all reads covering region of interest from RNA tumor BAM

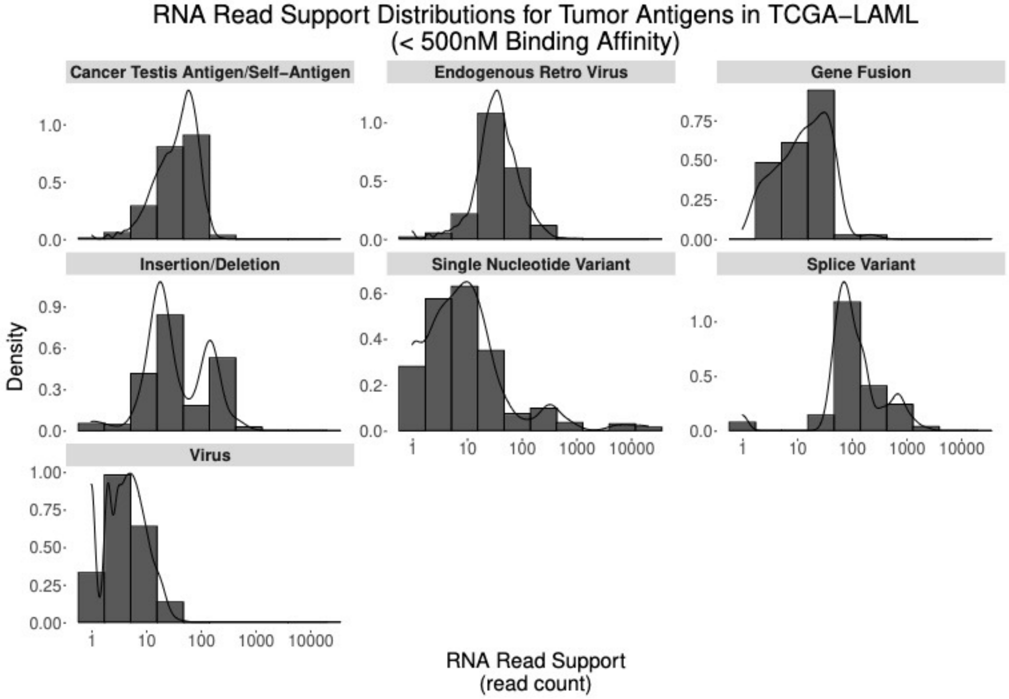
Filter to reads that are able to contain the entire peptide coding sequence

Count reads that contain ERV, CTA, or self-antigen peptide coding sequence

Predicted tumor antigen features in Acute Myeloid Leukemia





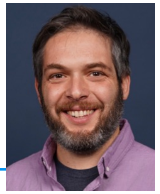


PIRL

Vensko et al. (2023) *Bioinformatics* 39(6):btad322

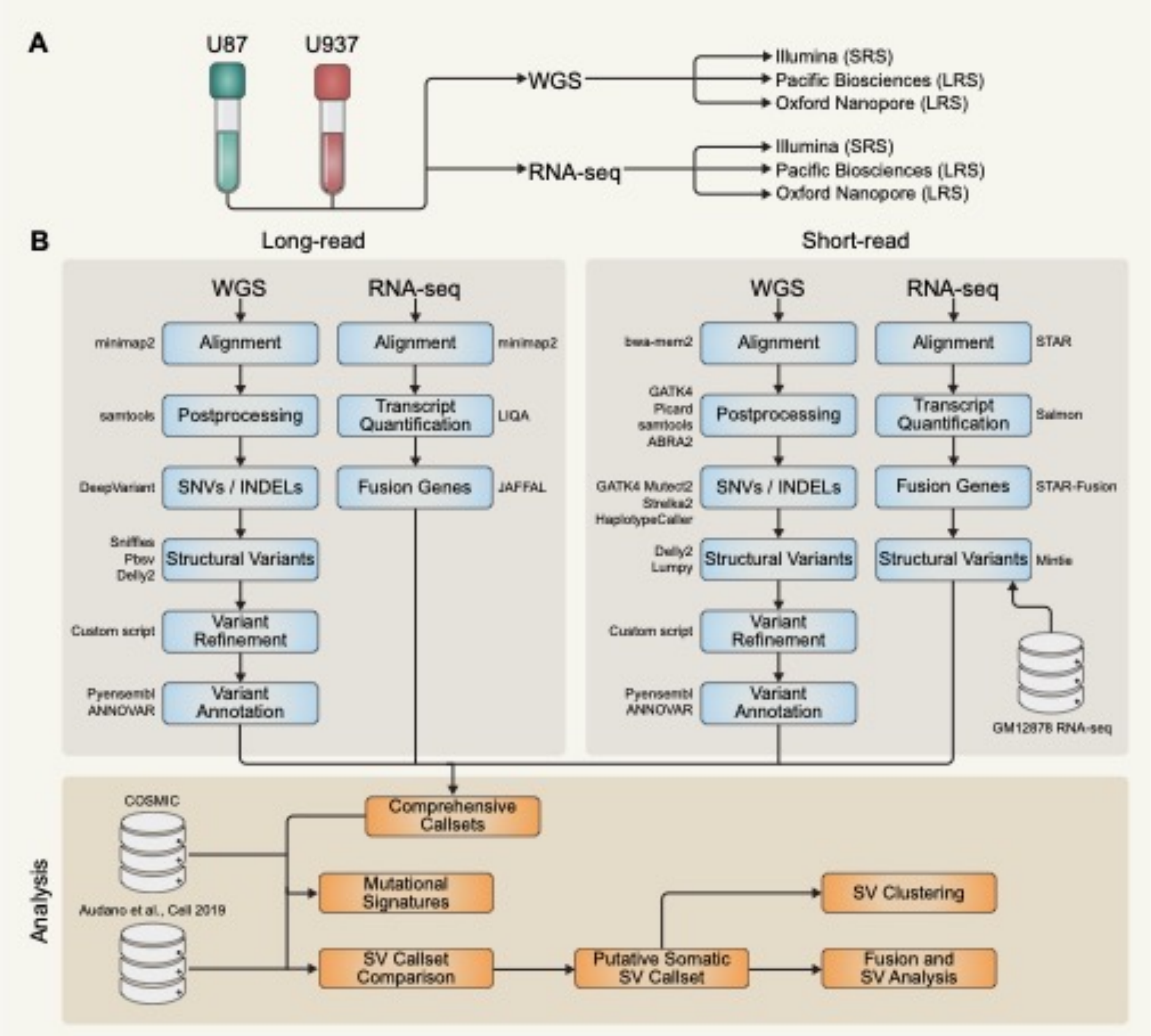
UNC SCHOOL OF MEDICINE

Long read sequencing for improved antigen detection



Alex Rubinsteyn

Andy Lee



PIRL

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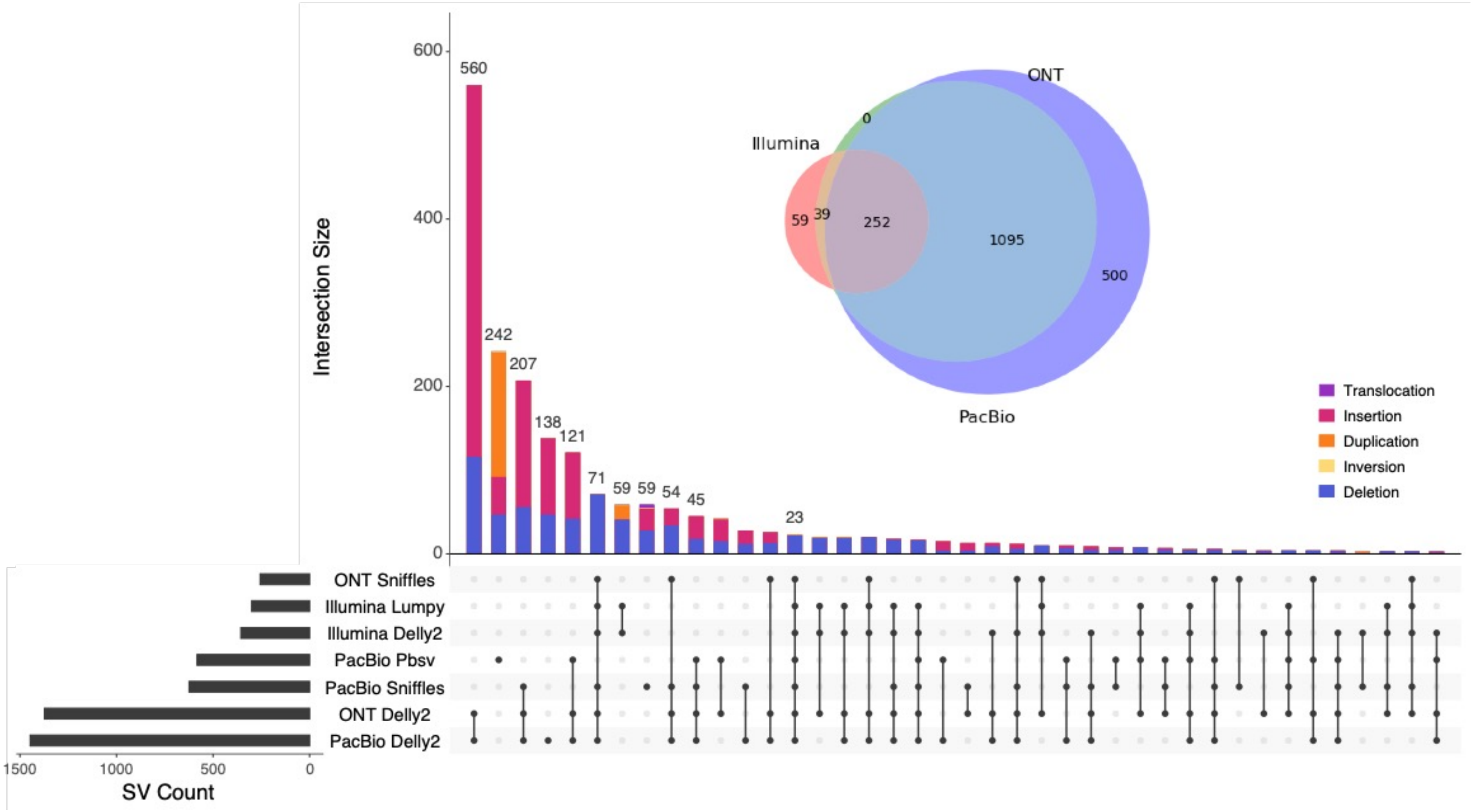

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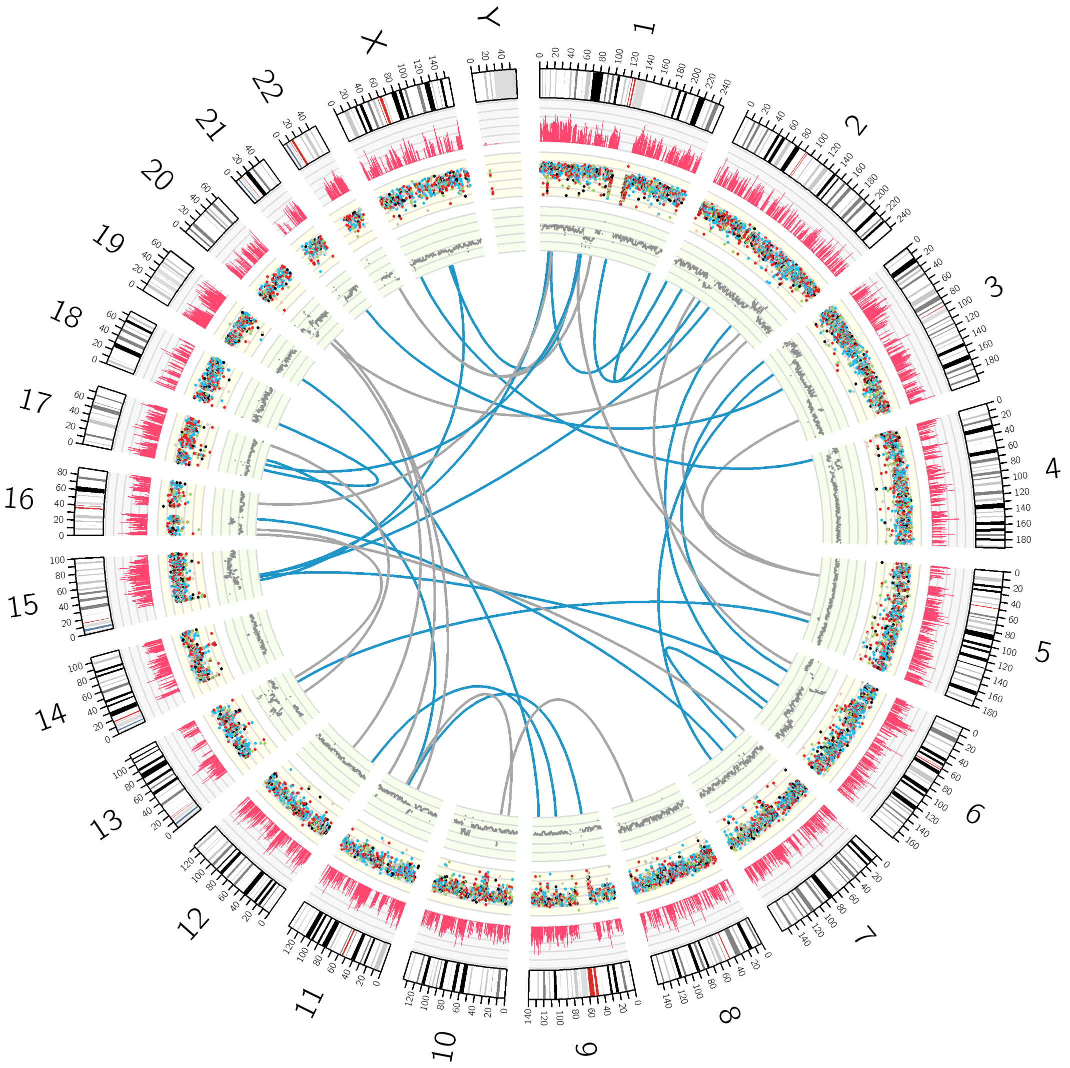


Tracks (from the outermost band)

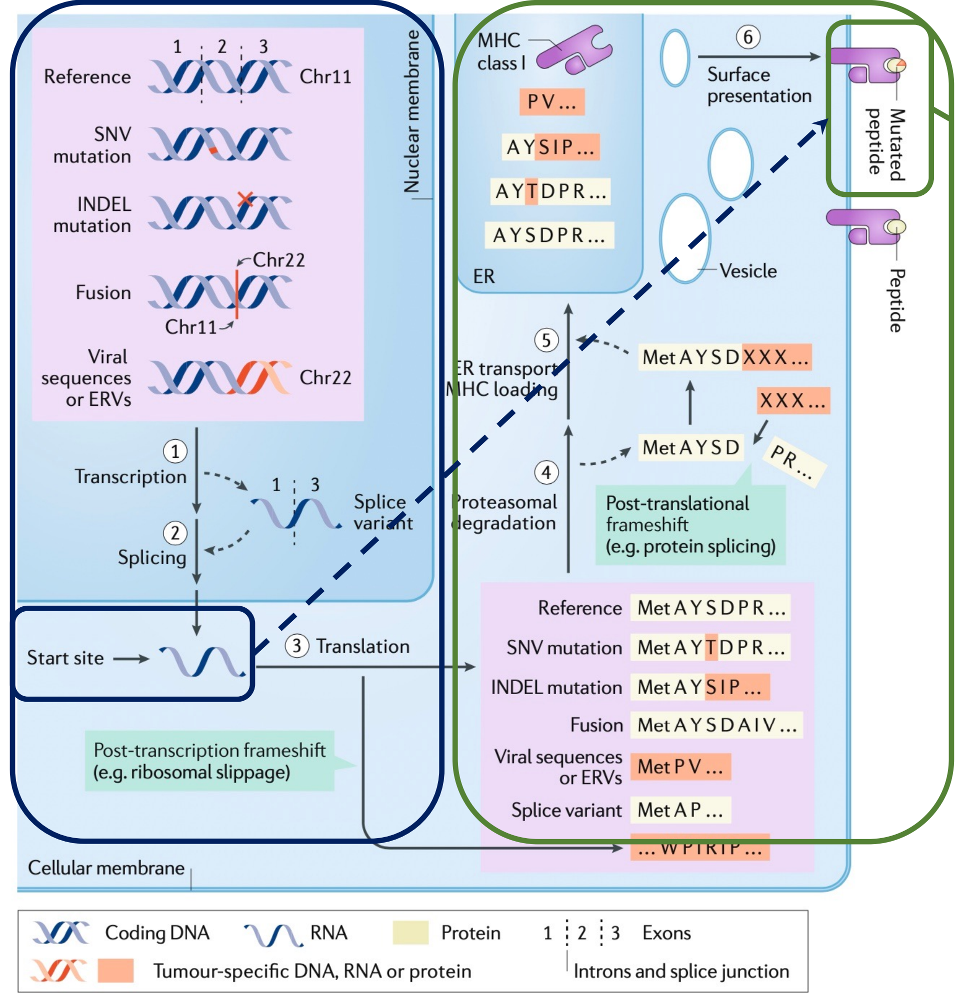
1. Cytobands
2. mRNA expression in TPM (log10)
3. Inter-mutation (SNV) distance (log10)
4. Sequencing depth
5. Translocations

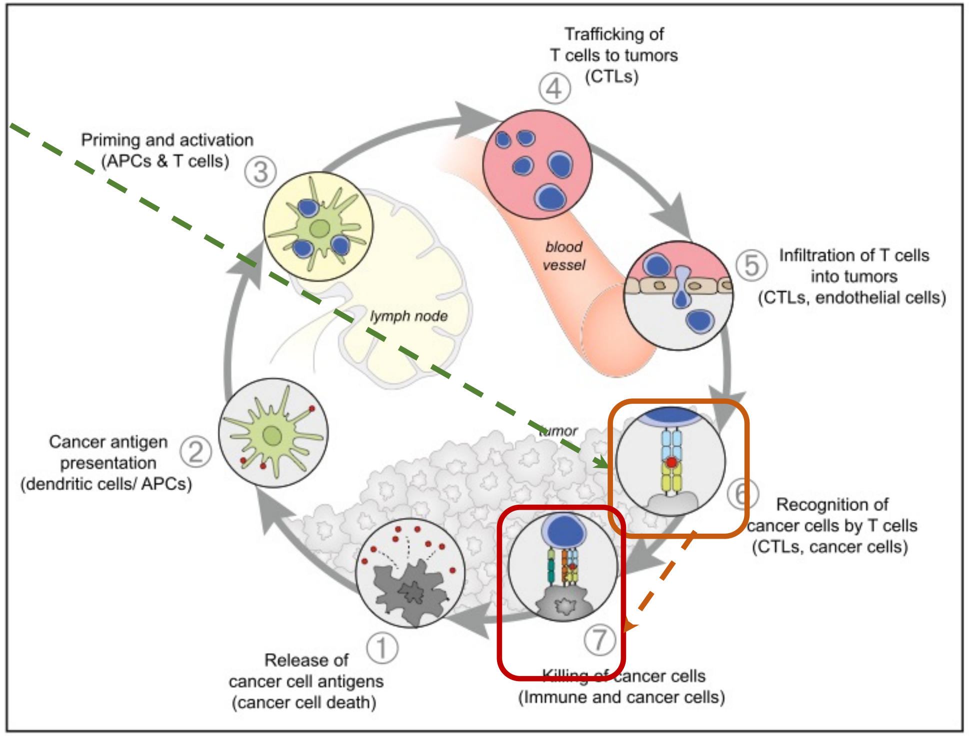
SBS Types

- C>A
- C>G
- C>T
- T>A
- T>C
- T>G

Translocations

- Long-read only
- Short and long read





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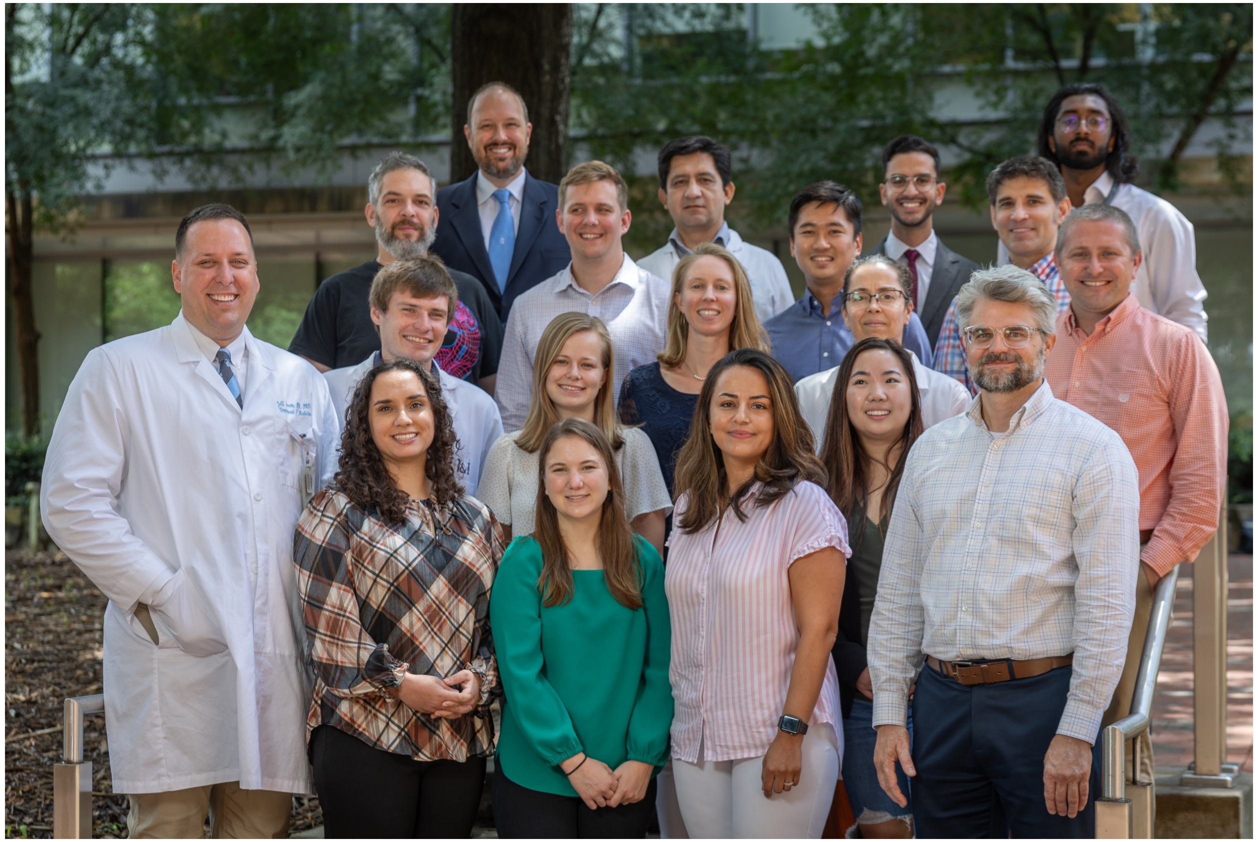
Smith C. et al. (2019) *Nature Reviews* Cancer; Chen & Mellman (2013) *Immunity* 39:1

Thank you!

Personalized Immunotherapy Research Lab (PIRL)



https://pirl.unc.edu/

TGCA IRWG

Institute for Systems Biology

Vésteinn Thorsson
Ilya Shmulevich
(& many others…)

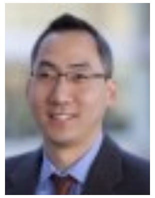
Breast Cancer

Jon Serody

Lisa Carey

Chuck Perou

Bladder Cancer



William Kim
Ryoichi Saito

Funding

NIH NATIONAL CANCER INSTITUTE

Bladder Cancer Advocacy Network BCAN Leading the way to awareness and a cure

susan G. komen

CRI Cancer Research Institute

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