CEDAR
Cancer Epitope Database and Analysis Resource

Neoepitope & Prostate Cancer Meta-analyses

cedar.iedb.org

Presented by: Zeynep Koşaloğlu-Yalçın, Instructor

Introduction

- When we first started CEDAR, we curated two prototype datasets:
  - **Prostate cancer antigens** (shared, non-mutated targets in “cold” tumors)
  - **Neoepitopes** (mutation-derived targets in highly mutated tumors)

- These represent **orthogonal categories**:
  - One rooted in well-characterized tumor-associated antigens
  - One focused on emerging targets for **personalized neoepitope vaccines**

- **We performed meta-analyses on both datasets**
- **<u>Goals:</u>**
  - Illustrate CEDAR capabilities
  - Identify strengths and knowledge gaps

Inventory of Epitopes from Prostate Antigens

Protein	Abbreviation	Species	Proteome Accession	References[1]	Protein Lengths	Epitopes[2]						
						Total[4]	Host Human	Host Mouse	B Cell	T Cell	T Cell Class I	T Cell Class II
Prostatic acid phosphatase	PAP; PAcP	human, mouse, rat	P15309, Q8CE08, A0A0G2K4B4	**30**	**386 381 381**	**67**	**35**	**34**	**11**	**64**	**31**	**33**
Prostate-specific antigen	PSA, KLK3	human	P07288	**44**	**261**	**78**	**39**	**47**	**52**	**51**	**33**	**18**
Prostate-specific membrane antigen	PSMA	human, mouse	Q04609 O35409	**32**	**750 752**	**51**	**39**	**17**	**34**	**34**	**27**	**6**
Prostein (Solute carrier family 45 member 3)	PROS[3]	human, mouse, rat	Q96JT2 Q8K0H7 D3ZPP5	**5**	**553 553 564**	**42**	**42**	**0**	**38**	**4**	**4**	**0**
Prostate stem cell antigen	PSCA	human	O43653	**6**	**114**	**18**	**18**	**1**	**7**	**17**	**17**	**0**
Metalloreductase STEAP1	STEAP	human, mouse	Q9UHE8 Q9CWR7	**8**	**339 339**	**15**	**7**	**10**	**0**	**15**	**13**	**2**
Transient receptor potential cation channel subfamily M member 8	Trp-p8	human, mouse	Q7Z2W7 Q8R4D5	**2**	**1104 1104**	**2**	**1**	**1**	**0**	**2**	**2**	**0**
TCR gamma alternate reading frame protein	TARP	human	A2JGV3.1	**5**	**58**	**5**	**6**	**0**	**0**	**5**	**3**	**2**
Total				**132**		**278**	**187**	**110**	**142**	**192**	**130**	**61**

[1] Does not include papers with MHC assays only
[2] Total includes B cell and T cell epitopes only
[3] PROS is used an abbreviation for Prostein (Solute carrier family 45 member 3)
[4] Papers might describe more than one protein

Data refer to epitope structures associated with positive data

T cell assay types for epitopes from top antigens

	Antigen Name	Parent Protein	Total Tcell Assays	Assays with class I restriction	Assays with class II restriction	Class I restricted epitopes	Class II restricted epitopes
T cell assays[1]	PSA	P07288	314	222	92	30	19
	PSMA	Q04609	115	89	20	25	6
	PAP	P15309	265	146	119	28	33
	PSCA	O43653	49	49	0	17	0
	Other[3]		121	75	45	16	4
Tetramer	PSA	P07288	28	26	2	7	1
	PSMA	Q04609	2	2	0	1	0
	PAP	P15309	5	5	0	3	0
	PSCA	O43653	0	0	0	0	0
	Other		4	4	0	3	0
MHC ligand[2]	PSA	P07288	93	65	28	25	8
	PSMA	Q04609	102	86	16	42	5
	PAP	P15309	134	82	61	41	28
	PSCA	O43653	23	22	1	12	1
	Other		143	80	63	50	59
Total			**1398**	**953**	**447**	**300**	**164**

[1] Includes tetramer assays
[2] Includes MHC binding assays and MHC ligand elution (MHCLE) assays
[3] Includes numbers for PSCA, STEAP, Trp-p8, and TARP

Cytokine assays by antigen

Protein	IFNg	TNFa	IL-10	IL-12	IL-13	IL-2	IL-4	IL-5	GrB
PSA	208	9	6	8	2	5	7	6	2
PSMA	101					2			
PAP	274	1							4
PSCA	43								

Note: The total number of assays can be greater than the number of epitopes as there are multiple assays for each cytokine (e.g. ELISA, ELISPOT, ICS, etc.).

Conclusion for Prostate-Specific Antigens

Identified important **knowledge gaps**

- literature is skewed towards **PAP**, **PSA**, and **PSMA** leaving the other 5 antigens under-characterized
- T cell assays are mainly restricted to MHC class I
- cytokines other than IFNg are not well studied

Review > Hum Immunol. 2023 Sep 5:S0198-8859(23)00313-0.
doi: 10.1016/j.humimm.2023.08.145. Online ahead of print.

A meta-analysis of epitopes in prostate-specific antigens identifies opportunities and knowledge gaps

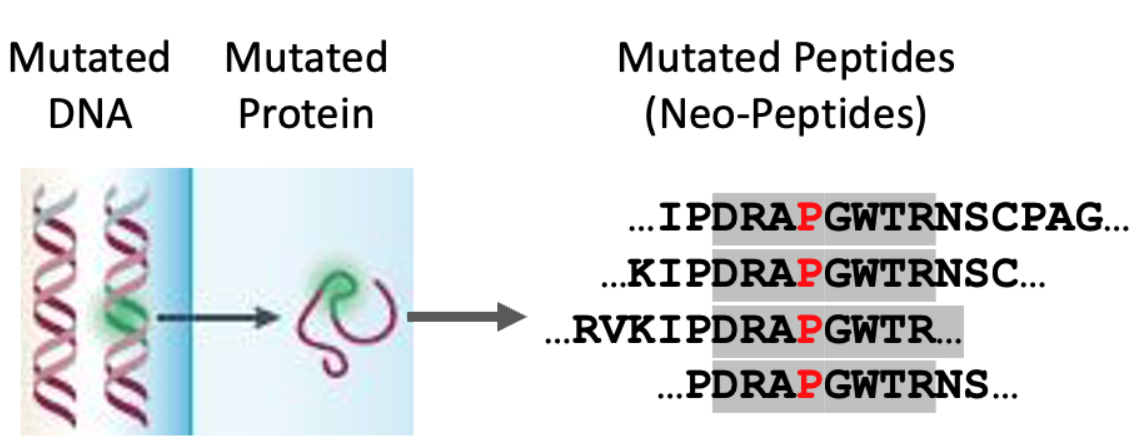
Gabriele Foos [1], Nina Blazeska [1], Morten Nielsen [2], Hannah Carter [3], Zeynep Kosaloglu-Yalcin [1], Bjoern Peters [4], Alessandro Sette [5]

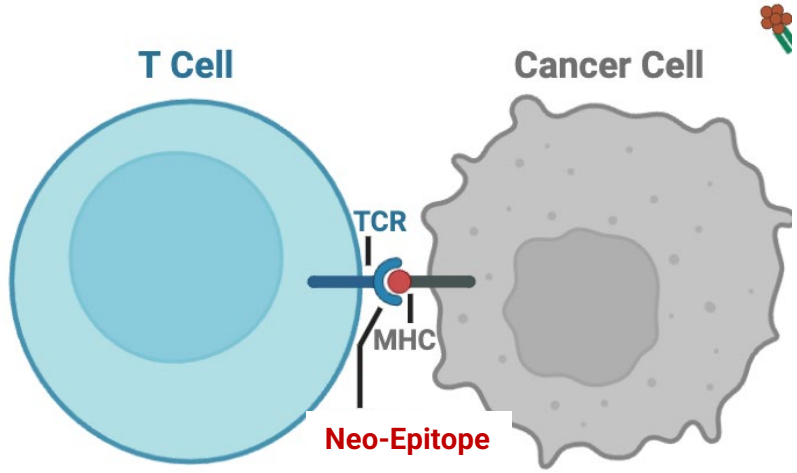
Affiliations + expand

PMID: 37679223 DOI: 10.1016/j.humimm.2023.08.145

Read the published article here -
https://pubmed.ncbi.nlm.nih.gov/37679223/

Neoantigens

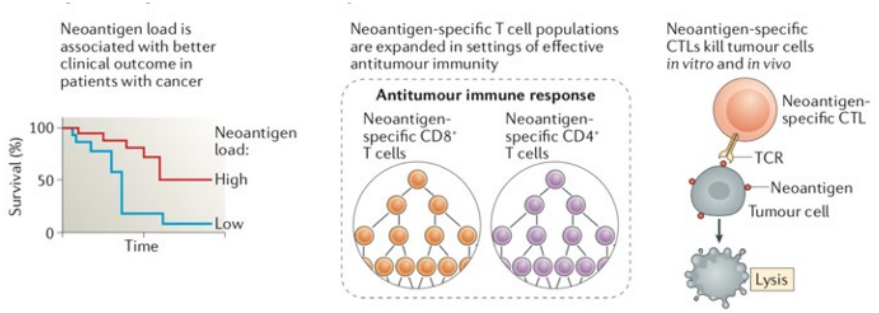




- Neo-epitopes are generated by somatic mutations and are highly tumor-specific

Neo-Epitopes: Clinically Valuable, Computationally Challenging

Clinical Relevance



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER IMMUNOTHERAPY

A functional identification platform reveals frequent, spontaneous neoantigen-specific T cell responses in patients with cancer

Aaron M. Miller[1,2]†, Zeynep Koşaloğlu-Yalçın[3]†, Luise Westernberg[3], Leslie Montero[1], Milad Bahmanof[1], Angela Frentzen[3], Manasa Lanka[3], Ashmitaa Logandha Ramamoorthy Premlal[3], Gregory Seumois[1], Jason Greenbaum[3], Spencer E. Brightman[1], Karla Soria Zavala[1], Rukman R. Thota[1], Martin S. Naradikian[1], Samir S. Makani[2], Scott M. Lippman[2], Alessandro Sette[3], Ezra E. W. Cohen[2], Bjoern Peters[3,4]*†, Stephen P. Schoenberger[1,2]*†

Computational Challenge

Cell

Resource

Key Parameters of Tumor Epitope Immunogenicity Revealed Through a Consortium Approach Improve Neoantigen Prediction

Graphical Abstract

Authors

Daniel K. Wells, Marit M. van Buuren, Kristen K. Dang, ..., Ton N. Schumacher, Pia Kvistborg, Nadine A. Defranoux

LETTER

doi:10.1038/nature24473

A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy

Marta Łuksza[1], Nadeem Riaz[2,3], Vladimir Makarov[3,4], Vinod P. Balachandran[5,6,7], Matthew D. Hellmann[7,8,9], Alexander Solovyov[10,11,12,13], Naiyer A. Rizvi[14], Taha Merghoub[7,15,16], Arnold J. Levine[1], Timothy A. Chan[2,3,4,7], Jedd D. Wolchok[7,8,15,16] & Benjamin D. Greenbaum[10,11,12,13]

Research Objective

Systematically characterize experimentally validated neo-epitopes to identify key features of immunogenicity and improve neoantigen prediction

Neo-Epitope Data in CEDAR

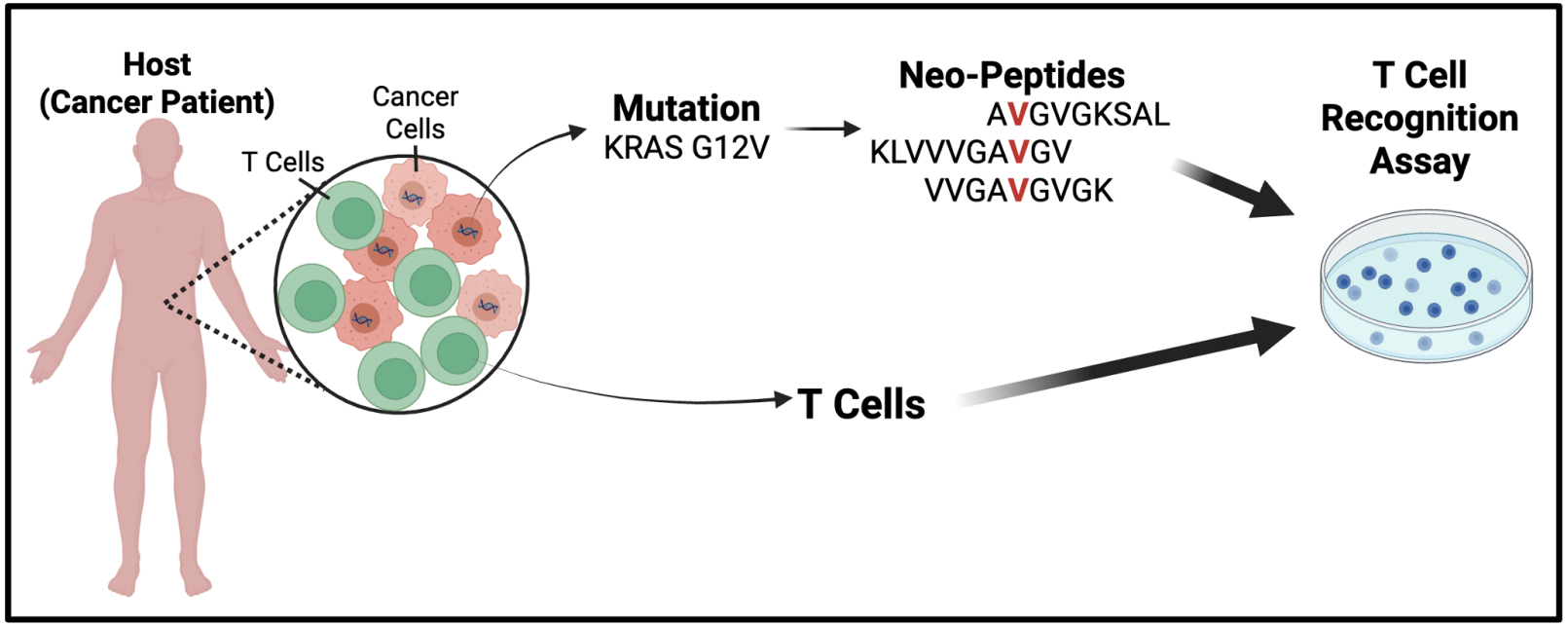
- Focused on human neo-peptides arising from **single nucleotide variants (SNVs)**
- Dataset includes:

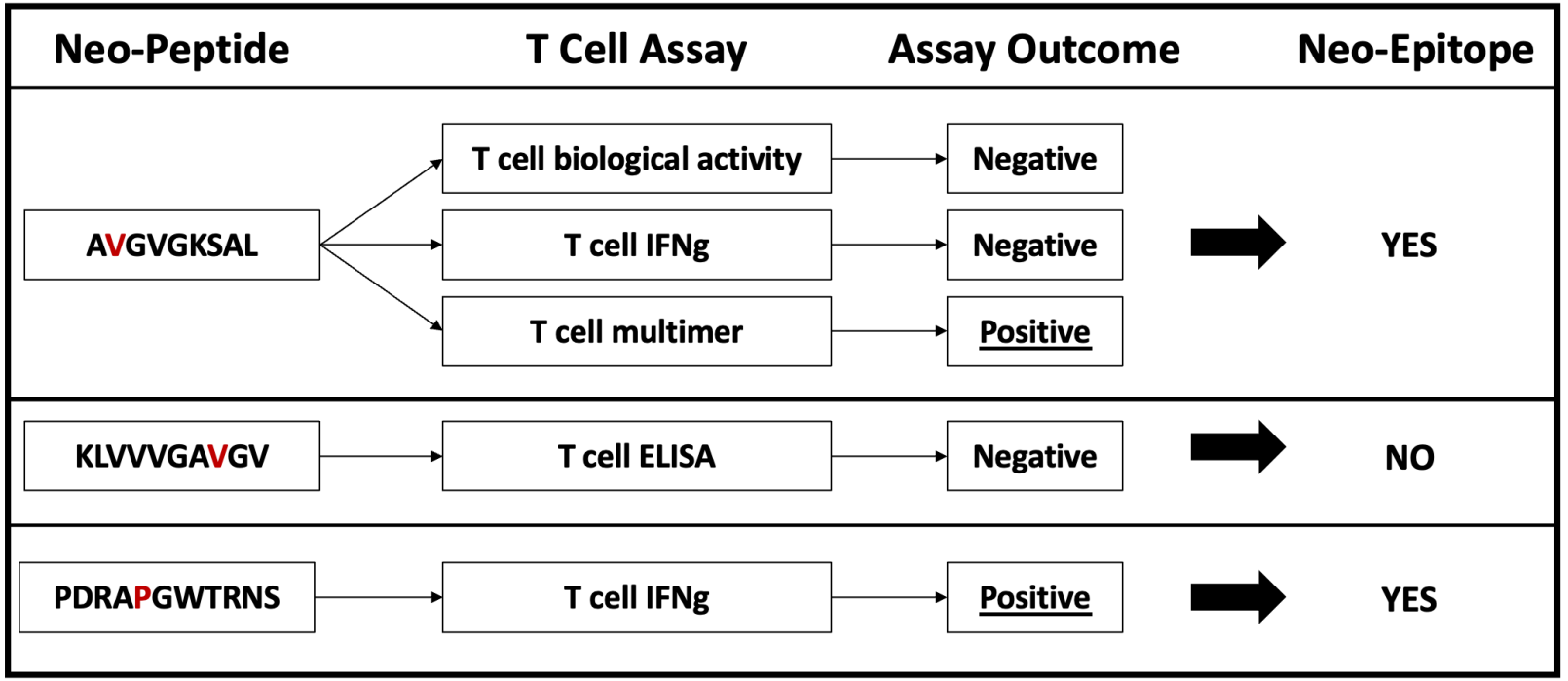
  16,672 neo-peptides from

  13,456 mutations in

  7,834 source proteins, tested

  in **20,701 T cell assays** from **180 studies** across **28 cancer types**
- A peptide was classified as a **neo-epitope** if **≥1 assay** showed a positive T cell response
- **13%** of peptides were validated as neo-epitopes; **87%** showed no T cell reactivity

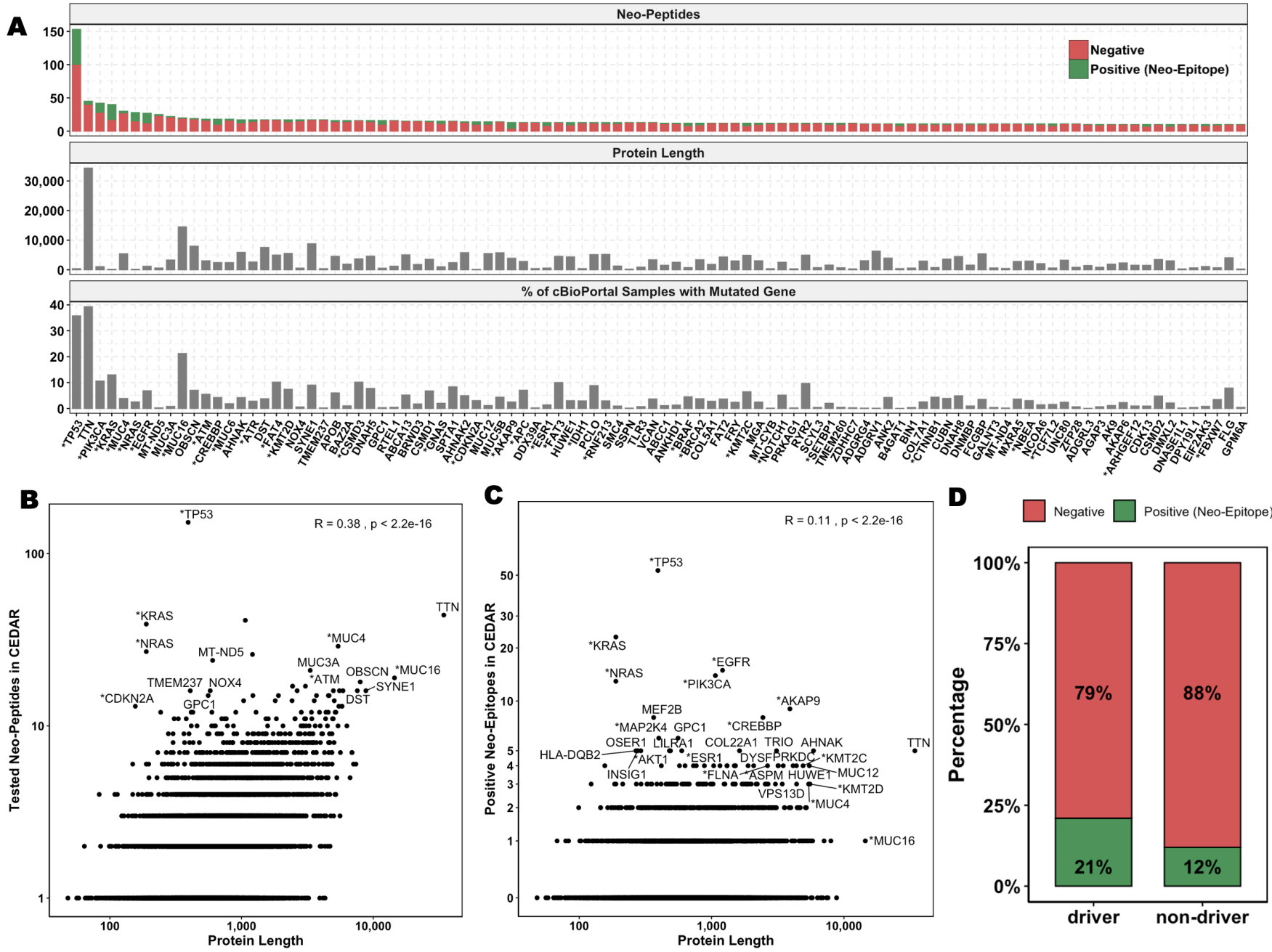




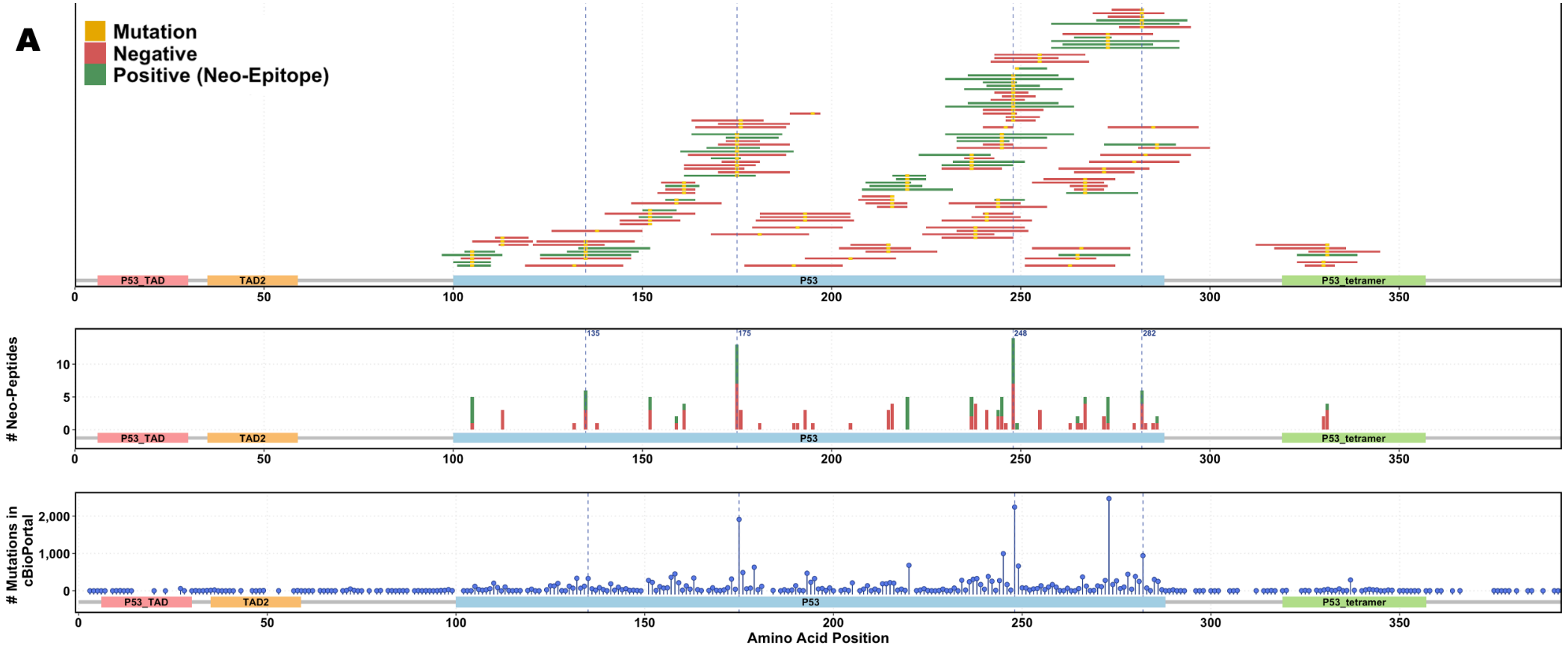
Neo-Epitopes Are Enriched in Driver Genes

- Frequently tested proteins were often **large** or **highly mutated** in tumors
- Large proteins tend to produce **more neo-peptides**, but not more **immunogenic neo-epitopes**
- **Driver genes** yielded **significantly more** validated neo-epitopes than non-driver genes

➔ Neo-epitope enrichment reflects **biological relevance**, not just mutation frequency or protein size

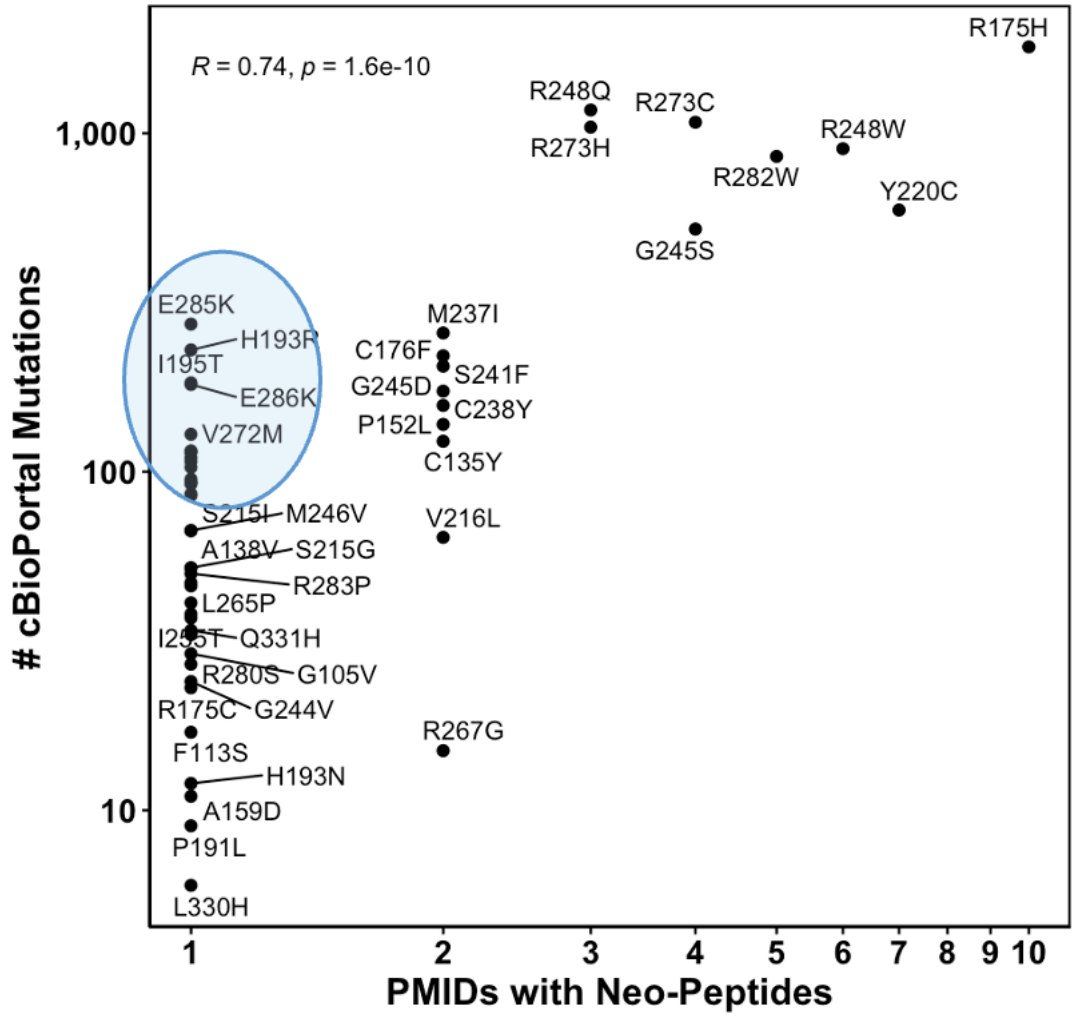


TP53 is a major source of neo-epitopes



- **TP53** is the most frequently mutated gene in human cancers and yields the most neo-epitopes
- CEDAR contains **152 neo-peptides** from **68 mutations** at **47 positions** within p53
- **35%** of neo-peptides were validated as **neo-epitopes**, significantly higher than the global average (13%)
- Neo-epitopes are concentrated in the **DNA-binding domain)**
- Most originate from known **mutation hotspots** at positions **135, 175, 248, and 282**

Some frequently occurring TP53 mutations appear to be understudied



Neo-epitope landscape across cancer types

- Cancers with high mutation burdens contributed the most neo-peptides
- Mutational burden correlated with number of tested peptides (R = 0.51)
- Weak correlation between mutational burden and T cell recognition (R = 0.15)

➔ more mutations do not necessarily lead to increased T cell recognition

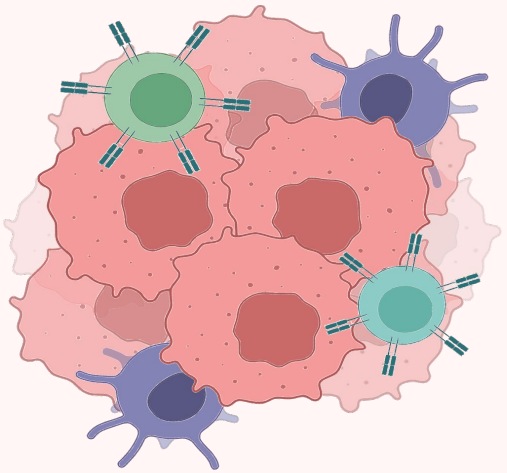
- After **normalization** by mutation burden, neo-epitope fractions for some cancers **substantially changed**

➔ low neo-epitope positivity may stem from **dilution by a high number of non-immunogenic mutations** rather than a lack of immunogenic potential

➔ mutation **quality over quantity**

Conclusions

- We performed the **largest meta-analysis to date** of experimentally tested neo-peptides
- we uncovered **patterns, biases** and potential **research gaps**



Cancer Immunology, Immunotherapy (2025) 74:362
https://doi.org/10.1007/s00262-025-04209-7

RESEARCH

Check for updates

A meta-analysis of experimentally validated neo-epitopes: patterns, biases, and opportunities

Alessandro Sette[1,2] · Ibel Carri[1] · Daniel Marrama[1] · Angela Frentzen[1] · Jarjapu Mahita[1] · Nina Blazeska[1] · Randi Vita[1] · Morten Nielsen[3] · Yat-Tsai Richie Wan[3] · Hannah Carter[2] · Stephen Schoenberger[4] · Bjoern Peters[1,2] · Zeynep Koşaloğlu-Yalçın[1]

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- Hannah Carter

Denmark Technical University

- Morten Nielsen
- Yat-Tsai Wan