



A meta-analysis of defined epitopes from prostate specific antigens

Opportunities and knowledge gaps

cedar.iedb.org

Presented by: Alessandro Sette, IEDB Principal Investigator

Introduction


- Cancer Epitope Database Analysis Resource (CEDAR):
 - Novel database initiative, to eventually host all cancer-related epitope data (Koşaloğlu-Yalçın et al., Front Immunol. 2021)
 - Initiated in 2021, leveraging experience of nearly 20 years by the sister database IEDB (Vita et al., Nucleic Acids Res. 2019)
- In parallel with database development, we decided to curate two prototype categories:
 - Prostate cancer antigens
 - Neoepitopes
- Orthogonally distinct data sources, one derived from well-defined and non-mutated antigens associated with “cold” tumors, and one associated with highly mutated tumors, targeted by neoepitope vaccines
- Here we present a meta-analysis of prostate associated antigens
- Goals:
 - Illustrate CEDAR capabilities at this early stage and to solicit feedback
 - Identify strengths and knowledge gaps related to the prostate antigens

Definition of reports associated with prostate-specific antigens


- Text classifier identifies relevant cancer-related papers (Wang, BMC Bioinformatics 2007)
- As of 9/15/22, of a total of 11,442 cancer-related papers, 395 were classified as related to prostate associated antigens
- Processed 96.5% of them; after abstract review 222 were potentially curatable and 165 were found to contain curatable information.
- A manual literature search for prostate-specific antigens identified eight major prostate-specific antigens
- All represented in the curated papers classified as prostate antigens
- Analysis focuses on these 8 prostate-specific antigens, and excludes antigens associated with, but not specific for, prostate cancer

CEDAR Home Page – cedar.iedb.org


START YOUR SEARCH HERE

Epitope ? 


Any
 Linear peptide
Exact Matc
 Discontinuous
 Non-peptidic

Assay ? 


T Cell
 B Cell
 MHC Ligand
Ex: Cytotoxicity
Outcome: Positive Negative

Epitope Source ? 


Antigen
Cancer-associated antigens:
 Neoantigen
 Viral antigen
 Germline/Self/Host antigen
 Other antigens from same reference

MHC Restriction ? 

Any
 Class I
 Class II
 Non-classical
Ex: HLA-A*02:01

Host ? 

Any
 Human
 Mouse
 Non-human primate
 Ex: C57BL/6

Cancer ? 

Type
Stage
Exposure
 Any
 Naturally occurring disease
 Animal model of cancer
 Vaccination

- Six main search panes allow for the selection of specific criteria
- Queries can be performed by epitope(s) of interest (e.g., linear B-cell epitopes from specific protein)
- Queries can be used to narrow down the data to certain subsets of the data (e.g., humans with pancreatic cancer)

CEDAR Result Page

Query: T cell epitopes of prostate antigens

PENDING FILTERS

Search Reset

Filter Options ?

T Cell

Epitope ?

Any

Linear peptide

Length

Sequence

Discontinuous

Non-peptidic

3D structure assays

Amino acid modification

Epitope Source ?

Organism

Ex: Influenza, peanut

Antigen

Prostate-specific antigen

Cancer-associated antigens:

Neoantigen

Viral antigen

Germline/Self/Host antigen

Other antigens from same reference

TCR ?

Has TCR sequence

Type

Any Type

Paired chains only

CURRENT FILTERS: X | Antigen: Prostate-specific antigen [P07288] (PSA) (Homo sapiens (human)) X | Include Positive Assays X | No B cell assays X | No MHC assays

Epitopes (46)	Antigens (1)	Assays (322)	Receptors (1)	References (46)
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46 Records Found

CEDAR ID	Epitope	Antigen	Organism	# References	# Assays
989936	KLQCVDLHV	Prostate-specific antigen	Homo sapiens (human)	13	52
119196	VISNDVCAQV	Prostate-specific antigen	Homo sapiens (human)	10	41
1637461	FLTPKKLOCV	Prostate-specific antigen	Homo sapiens (human)	9	25
1860817	CYASGWGSI	Prostate-specific antigen	Homo sapiens (human)	6	14
23596	HCIRNKSVI	Prostate-specific antigen	Homo sapiens (human)	5	21
1714010	HYRKWIKDTI	Prostate-specific antigen	Homo sapiens (human)	5	12
119512	QVFSVSHSFPPLVD	Prostate-specific antigen	Homo sapiens (human)	3	5
1391978	VLVHPQWV	Prostate-specific antigen	Homo sapiens (human)	3	4
1872156	GVLGGITSWGSEPCALPERP	Prostate-specific antigen	Homo sapiens (human)	3	32
1872916	LQCVDLHVISNDVCAQVHPQ	Prostate-specific antigen	Homo sapiens (human)	3	28
23597	HCIRNKSIVL	Prostate-specific antigen	Homo sapiens (human)	2	8
1872209	HPQKVTKFML	Prostate-specific antigen	Homo sapiens (human)	2	6
1972709	GVLVHPQWV	Prostate-specific antigen	Homo sapiens (human)	2	6
39836	LTDVAVKMDL	Prostate-specific antigen	Homo sapiens (human)	1	5
1092852	DLPTQEPAL	Prostate-specific antigen	Homo sapiens (human)	1	1
1639804	MLLRLSEPA	Prostate-specific antigen	Homo sapiens (human)	1	1
1643651	AELTDAVKVMDLPTQ	Prostate-specific antigen	Homo sapiens (human)	1	1
1650003	DDSSDMLLRLSEP	Prostate-specific antigen	Homo sapiens (human)	1	1
1658469	FQVSHSFPPLVD	Prostate-specific antigen	Homo sapiens (human)	1	1
1667944	IRNKSIVLLGRH	Prostate-specific antigen	Homo sapiens (human)	1	1
1670719	KKLQCVQLHVISM	Prostate-specific antigen	Homo sapiens (human)	1	1
1672234	KSVILLGRHSLFHP	Prostate-specific antigen	Homo sapiens (human)	1	1
1676376	LMLLRLSEPAELTDAVKV	Prostate-specific antigen	Homo sapiens (human)	1	1
1686603	PSLYTKVVHY	Prostate-specific antigen	Homo sapiens (human)	1	1
1688170	QKVTKFMLCAGRWTG	Prostate-specific antigen	Homo sapiens (human)	1	1

46 Records Found

- Five tabs show the number of records for Epitopes, Antigens, Assays, Receptors, and References.
- Result details can be accessed by clicking the relevant tabs.
- Query parameters can be adjusted by changing the search parameters on the left side of the page.

Query: T cell epitopes of prostate antigens

PENDING FILTERS

Search Reset

Filter Options ?

T Cell

Epitope ?

Any

Linear peptide

Length

Sequence

Discontinuous

Non-peptidic

3D structure assays

Amino acid modification

Epitope Source ?

Organism

Ex: influenza, peanut

Antigen

Prostate-specific antigen [1]

Cancer-associated antigens:

Neoantigen

Viral antigen

Germline/Self/Host antigen

Other antigens from same reference

CURRENT FILTERS: X Antigen: Prostate-specific antigen [P07288] (PSA) (Homo sapiens (human)) X Include Positive Assays X No B cell assays X No MHC assays

Epitopes (46)	Antigens (1)	Assays (322)	Receptors (1)	References (46)				
<div style="display: flex; justify-content: space-between;"> T Cell Assays (322) B Cell Assays (0) MHC Ligand Assays (0) 322 Records Found 25 Per Page Export Results </div>								
CEDAR ID	Reference	Epitope	Host	Immunization	Assay Antigen	Antigen Epitope Relation	MHC Restriction	Assay Description
16582984	J M Corman; Clin Exp Immunol 1998	QVFQVSHSFPHPLYD Prostate-specific antigen (88-102) Homo sapiens (human)	Homo sapiens (human)	Primary induction in vitro with QVFQVSHSFPHPLYD (Epitope)	QVFQVSHSFPHPLYD Prostate-specific antigen (88-102) Homo sapiens (human)	Epitope	HLA-DR4	3H-thymidine proliferation Positive-High
18141050	Elena N Klyushnenkova; Clin Cancer Res 2005	GVLQGITSWGSEPCA LPERP Prostate-specific antigen (221-240) Homo sapiens (human)	Mus musculus HLA-DRB1*15:01 Tg	Administration in vivo with Prostate-specific antigen (Source Antigen)	GVLQGITSWGSEPCA LPERP Prostate-specific antigen (221-240) Homo sapiens (human)	Epitope	HLA-DRB1*15:01	3H-thymidine proliferation Positive-High
16582993	J M Corman; Clin Exp Immunol 1998	KKLQCVQLHVISM Prostate-specific antigen Homo sapiens (human)	Homo sapiens (human)	Primary induction in vitro with KKLQCVQLHVISM (Epitope)	KKLQCVQLHVISM Prostate-specific antigen Homo sapiens (human)	Epitope	HLA-DR4	3H-thymidine proliferation Positive-Low
16582995	J M Corman; Clin Exp Immunol 1998	SLFHPEDTGQVFQ Prostate-specific antigen (79-91) Homo sapiens (human)	Homo sapiens (human)	Primary induction in vitro with SLFHPEDTGQVFQ (Epitope)	SLFHPEDTGQVFQ Prostate-specific antigen (79-91) Homo sapiens (human)	Epitope	HLA-DR4	3H-thymidine proliferation Positive-Low
16582996	J M Corman; Clin Exp Immunol 1998	FQVSHSFPHPLYD Prostate-specific antigen (90-102) Homo sapiens (human)	Homo sapiens (human)	Primary induction in vitro with FQVSHSFPHPLYD (Epitope)	FQVSHSFPHPLYD Prostate-specific antigen (90-102) Homo sapiens (human)	Epitope	HLA-DR4	3H-thymidine proliferation Positive-Low
1698213	Jonathan C Tong; Ann N Y Acad Sci 2002	QVFQVSHSFPHPLYD Prostate-specific antigen (88-102) Homo sapiens (human)	Mus musculus HLA-DR4 Tg	Administration in vivo with QVFQVSHSFPHPLYD (Epitope)	QVFQVSHSFPHPLYD Prostate-specific antigen (88-102) Homo sapiens (human)	Epitope	HLA-DRB1*04:01	3H-thymidine proliferation Positive
1808979	John A Gebe; Eur J Immunol 2003	QVFQVSHSFPHPLYD	Mus musculus HLA-DRB1*04:01 Tg	Administration in vivo with	QVFQVSHSFPHPLYD Prostate-specific	Epitope	HLA-DRB1*04:01	3H-thymidine proliferation

- Nine columns show the most relevant information about the individual assays
- Clicking the IEDB ID shows the detail of entire experimental process
- T-cell assay results can be downloaded in Excel by clicking the icon “export results” in the top right

Inventory of Epitopes from Prostate Antigens

Protein	Abbreviation	Species	Proteome Accession	References ¹	Protein Lengths	Epitopes ²							Epitopes		
						Total ⁴	Host Human	Host Mouse	B Cell	T Cell	T Cell Class I	T Cell Class II	MHC Binding	MHC Elution	Grand Total
Prostatic acid phosphatase	PAP; PACP	human,	P15309,	30	386	67	35	34	11	64	31	33	20	2	73
		mouse,	Q8CE08,		381										
		rat	A0A0G2K4B4		381										
Prostate-specific antigen	PSA, KLK3	human	P07288	44	261	78	39	47	52	51	33	18	22	1	82
Prostate-specific membrane antigen	PSMA	human, mouse	Q04609 O35409	32	750 752	51	39	17	34	34	27	6	23	1	60
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	6	2	48
Prostate stem cell antigen	PSCA	human	O43653	6	114	18	18	1	7	17	17	0	12	2	20
Metalloreductase STEAP1	STEAP	human,	Q9UHE8	8	339	15	7	10	0	15	13	2	2	5	19
		mouse	Q9CWR7		339										
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	5	9	14
TCR gamma alternate reading frame protein	TARP	human	A2JGV3.1	5	58	5	6	0	0	5	3	2	3	1	6
Total				132		278	187	110	142	192	130	61	93	21	322

¹ Does not include papers with MHC assays only

Data refer to epitope structures associated with positive data

² Total includes B cell and T cell epitopes only

³ PROS is used as an abbreviation for Prostein (Solute carrier family 45 member 3)

⁴ Papers might describe more than one protein

Conclusions I: Inventory of epitopes derived from eight main prostate antigens

- CEDAR contains a total of 322 positive epitopes studied in various assays (each epitope can be studied in more than one context):
 - 192 T cell assays
 - 142 B cell assays
 - 93 MHC binding assays
 - 21 MHC elution assays
- Number of epitopes vary by protein (highest with PAP, PSA and PSMA):
 - Number of epitopes correlates with number of publications ($r_s = 0.85032$, $p = 0.007$)
 - No correlation between protein length and epitopes ($r_s = -0.02381$, $p = 0.955$)

The value for correlation was calculated using <https://www.socscistatistics.com/tests/spearman/default2.aspx>

Note: the numbers will not add up to 322, some epitopes are measured in T cell and MHC assays.

T cell assay types for epitopes from top antigens

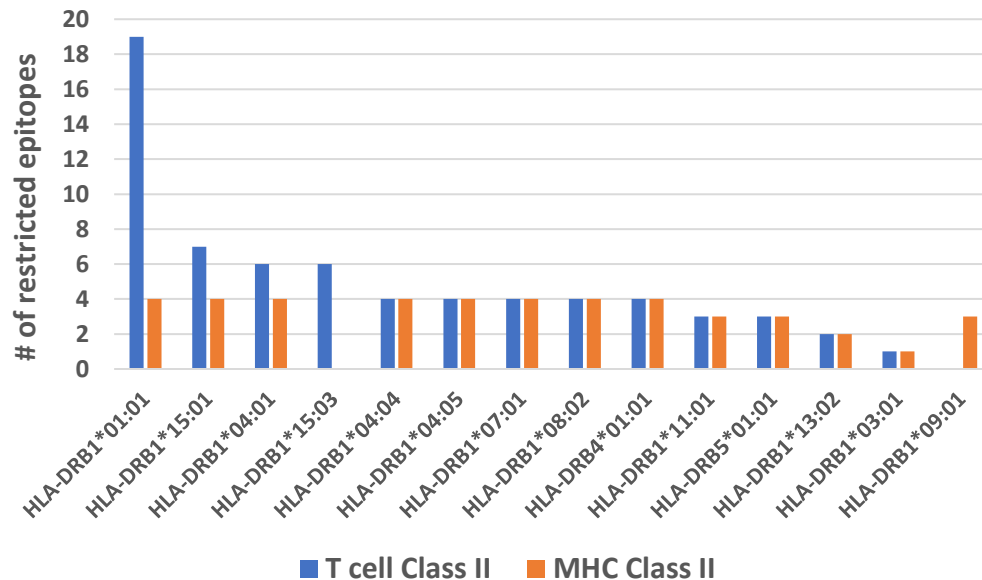
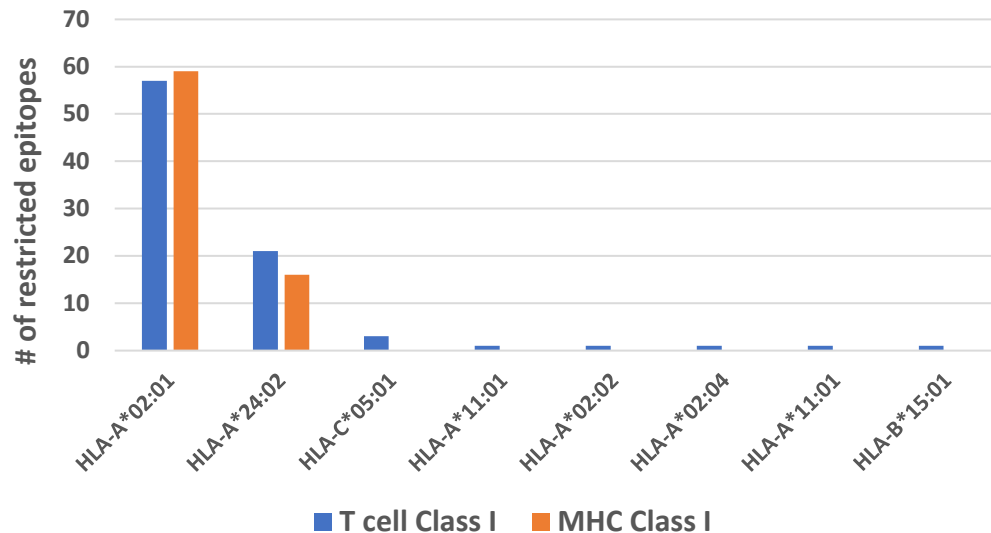
	Antigen Name	Parent Protein	Total Tcell Assays	Assays with class I restriction	Assays with class II restriction	Class I restricted epitopes	Class II restricted epitopes
T cell assays¹	PSA	P07288	314	222	92	30	19
	PSMA	Q04609	115	89	20	25	6
	PAP	P15309	265	146	119	28	33
	PSCA	O43653	49	49	0	17	0
	Other 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 ligand²	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

Class I and class II restrictions of epitopes from prostate antigens



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.).

Assay types of B cell epitopes

Protein	Monoclonal Response	Polyclonal Response	ELISA/ Western	Antigen Inhibition	SPR	Immuno Staining	IHC	Micro Array	In Vivo Assay	X-ray Crystallography	Biological Activity
PSA	64	26	40	11	6					5	4
PSMA	27	53	56	3		1	2	2	3		
PAP	2	37	24	3		1		2			
PSCA	0	24	23			1					

Note: The total number of assays can be greater than the number of epitopes

Assays involving recognition/killing of Prostate Tumor Cells

- Number of cytotoxicity assays vary by protein (5 to 24 assays)
- It is possible to search for tumor cell as antigen by exporting a search for cytotoxicity assays

Protein	Number of Cytotoxicity Assays
PSA	24
PSMA	5
PAP	18
PSCA	10

In vivo assays of epitopes from prostate antigens

- Very limited number of *in vivo* assays, measured by decreased disease, tumor burden, survival
- Most of the assays in xenograft models
- TRAMP is the only genetically engineered mouse model captured in CEDAR
- Possibly reflective of different anatomy of mouse and human prostate

Protein	Decreased Disease	Tumor Burden	Survival
PSA	3		
PSMA	6	2	
PAP	1	3	1
PSCA		1	

Receptor data captured for prostate antigens

TCR sequences

Epitope	Antigen	Antigen	Species	Response Type	MHC Allele	Type	Chain 1 CDR3	Chain 2 CDR3
KLQCVDLHV	PSA	P07288	Homo sapiens	T cell	HLA-A*02:01	$\alpha\beta$	CAVREEDYKL SF	ASSFRGPNLYTE AF

BCR sequences

Epitope	Antigen	Antigen	Species	Response Type	Type	Chain 1 CDR3	Chain 2 CDR3
H98, P99, L100, Y101, D116, H119, T143, K191, K194, F195, H248, Y249, R250, K251, W252, K254	PSA	P07288	Mus musculus	B cell	HL	ARADYGFNSGE AMDY	QQSNEDPYT
I25, W29, E30, C31, E32, K33, S35, Q36, W38, H82, D134, K137, Y153, K169, K170, C173, D175, G204, G205, N220, G221, V222	PSA	P07288	Mus musculus	B cell	HL	ARDGYRYFFDY	MQHLEYPVT
R45, G46, A48, N69, K70, L74, R77, L80, P83, G87, Q88, V89, Q91, V92, S93, H94, R125, S127, E128, F165	PSA	P07288	Mus musculus	B cell	HL	ARSGRLYFDV	QQTHEDPYT

Conclusions II: *in vitro* and *in vivo* assays

- T cell assays:
 - Mostly IFN γ assays
 - PSA is only protein with several other cytokine assays
 - Limited number of tetramer assays
- A total of 21 epitopes identified in MHC ligand elution (MHCLE) assays
- More diverse B cell assays:
 - Ratio of monoclonal/polyclonal varies by protein (PSA with most monoclonal)
 - Most assays are ELISA direct binding assays
 - Limited amount of *in vivo* assays (only PSMA has *in vivo* B cell assays)
- Limited number of *in vivo* tumor killing and *in vivo* assays
 - Lack of mouse models for prostate cancer
 - Most assays in xenograft models
- PSA only prostate-specific antigen with receptors (1 TCR and 3 BCR)
 - *Covid-2 has over 87000 TCR and 97 BCR captured*

Epitopes and Assays by Prostate Disease Type

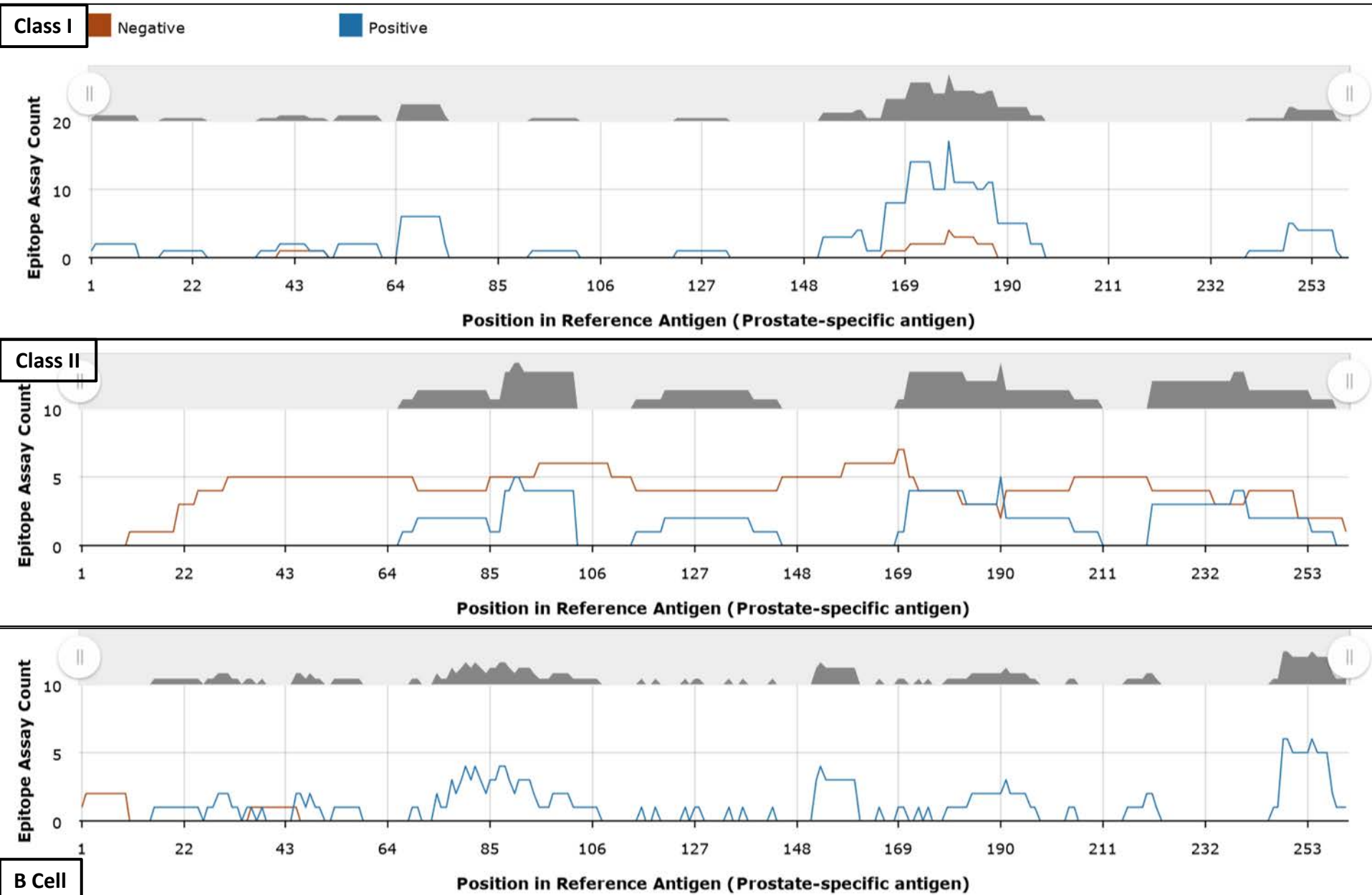
Disease State	Assay Type				Number of Epitopes			
	T Cell	B Cell	MHC	Total	T Cell	B Cell	MHC	Total
Prostate adenocarcinoma	78	41	3631	3747	31	40	3492	3565
Prostate cancer	415	264	0	679	167	193	0	360
Castration-resistant prostate carcinoma	72	90	0	162	35	29	0	64
Benign prostate phyllodes tumor	0	6	0	6	0	6	0	6
Lymphoepithelioma-like acinar prostate adenocarcinoma	0	6	0	6	0	6	0	6
Prostatitis	7	0	0	7	2	0	0	2
Prostate carcinoma	4	0	0	4	1	0	0	1

- Epitopes associated with six different prostate diseases captured in CEDAR
- Prostate adenocarcinoma and castration-resistant carcinoma are most studied
- Higher level category “prostate cancer” has the most T-cell and B-cell assays
- Gaps:
 - Staging not searchable
 - Stages are bulked and not always captured
 - Prostate cancer staging is complex, might need new options

Epitope distribution as revealed by Immunome Browser analysis (Immunodominance Patterns)

- ImmunomeBrowser tool (Dhanda et al., Bioinformatics. 2018)
 - Computes the number of assays and epitopes associated with each amino acid position along the antigen sequence
 - Visualizes all studied epitopes along the entire length of a prostate-specific antigen
 - Identifies immunodominant regions

PSA Immunodominance Pattern



Overall Conclusions

- Curation processed (96.5%) of prostate antigen papers and results from 165 papers are available in CEDAR
- The curated data provides the scientific community with a wealth of searchable information
- Knowledge gaps
 - Limited number of prostate epitopes with receptors available
 - Limited numbers of in vivo and tumor recognition assays captured
- Potential areas for CEDAR improvement:
 - Search function for cancer stages
 - Search function tumor cells as antigens
- Immunodominant regions identified for most prominent antigens with potential implication for vaccination strategies

Overall Conclusions

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

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Affiliations + expand

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

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