Bioinformatics and Biodiversity Conference 2020

Oral Presentation

Prediction of promiscuous T cell epitopes in Hepatitis B virus proteome as a starting point for designing immunotherapy and vaccine

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Abstract

Hepatitis B virus is endemic in Indonesia and causes a range of liver damage. Recently, the development of therapy aiming to improve immune response has gained a priority. T-cell immunity plays an essential role to control viral infections. Cytotoxic CD8+ T-cells are responsible for the elimination of virus-infected cells, while CD4+ T-cells are essential for the regulation and maintenance of immune responses and the production of cytokines. T-cells recognize peptides derived from the HBV proteins as a complex with HLA (human leukocyte antigen) on the surface of the infected cells. The strong link between HBV genotype and the ethnicity of the population suggests that immunotherapy needs to be based on the epitopes derived from the prevalent viral strain and presented by the prevalent HLA types in the related population. In this study, immunoinformatic prediction using netMHCpan and netMHCIIpan were used to identify T-cell epitopes from the major HBV genotypes in Indonesia. The likelihood that the predicted peptides will be processed inside the cells was assessed using the netCTLpan server. Other prediction tools housed in the IEDB server were employed to generate a consensus result. BLAST analysis was done to exclude epitopes that resemble human self-peptides. The epitope conservancy analysis and population coverage were carried out using tools in IEDB. The set of promiscuous epitopes that bind to HLA Class I and II predominant in the Indonesian population were identified. These epitopes could be used as a starting point to develop a new and more efficient vaccine and immunotherapies against HBV.

Keywords: immunoinformatics, hepatitis B virus, T-cell epitopes, human leukocyte antigen

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Prediction of promiscuous T cell epitopes in Hepatitis B virus proteome as a starting point for designing immunotherapy and vaccine

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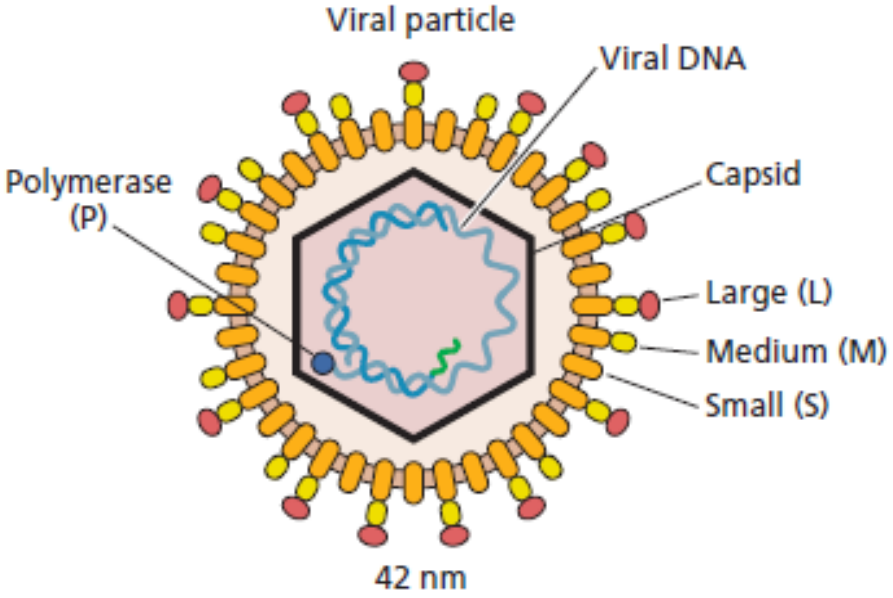
Hepatitis B Virus - Epidemiology

- Hepatitis B virus is the virus which infect liver cells.
- Major causes of liver inflammation world-wide
- Indonesia is moderate-high endemic region for HBV, prevalence 9.4%

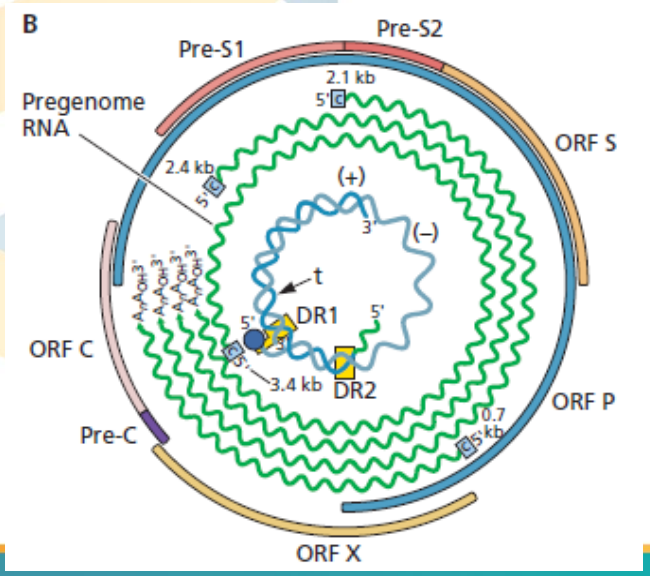
NIHRI, MOH, Republic of Indonesia, 2010: 38-43

HBV structure, genome, and replicative cycle



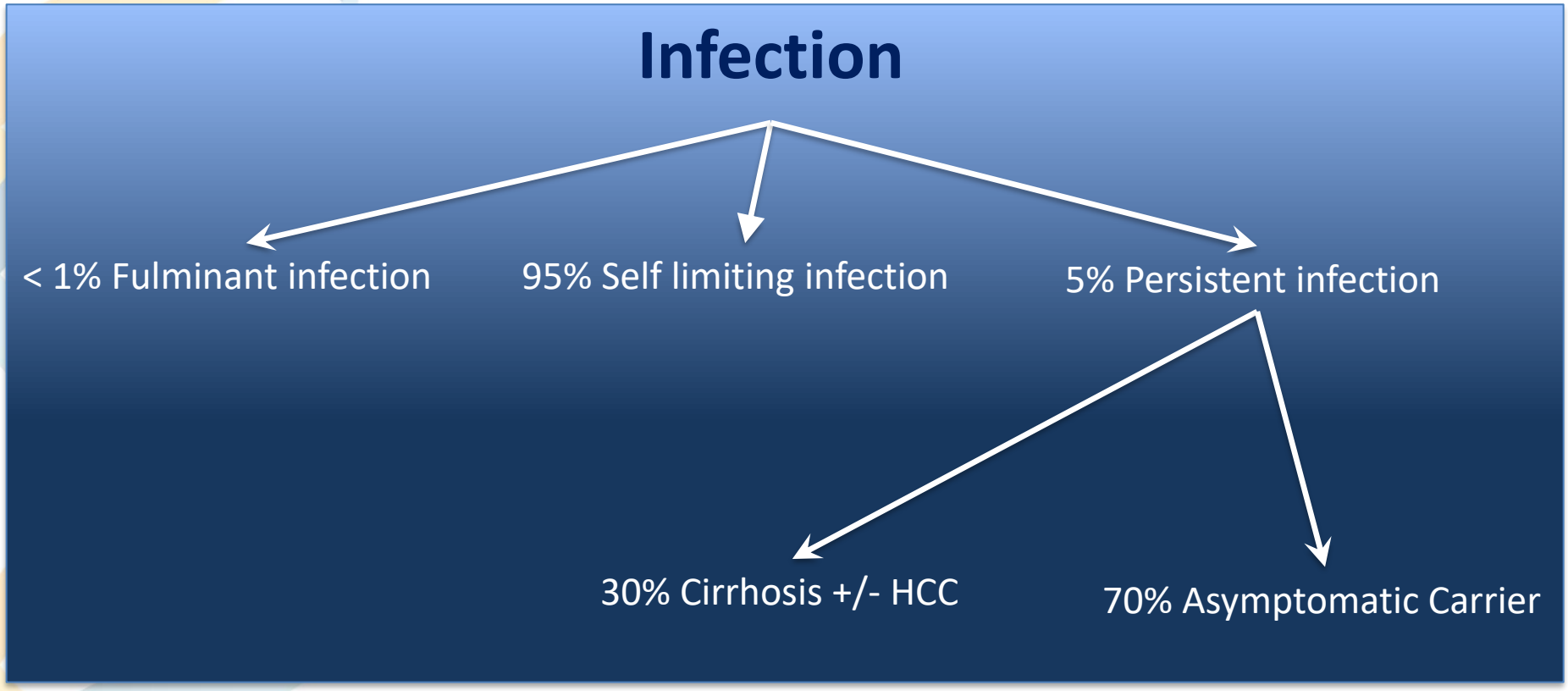
- Envelope: surface protein – large, medium and small
- Capsid protein – surrounding the genome
- Polymerase protein - attached to the genome

Virus genome



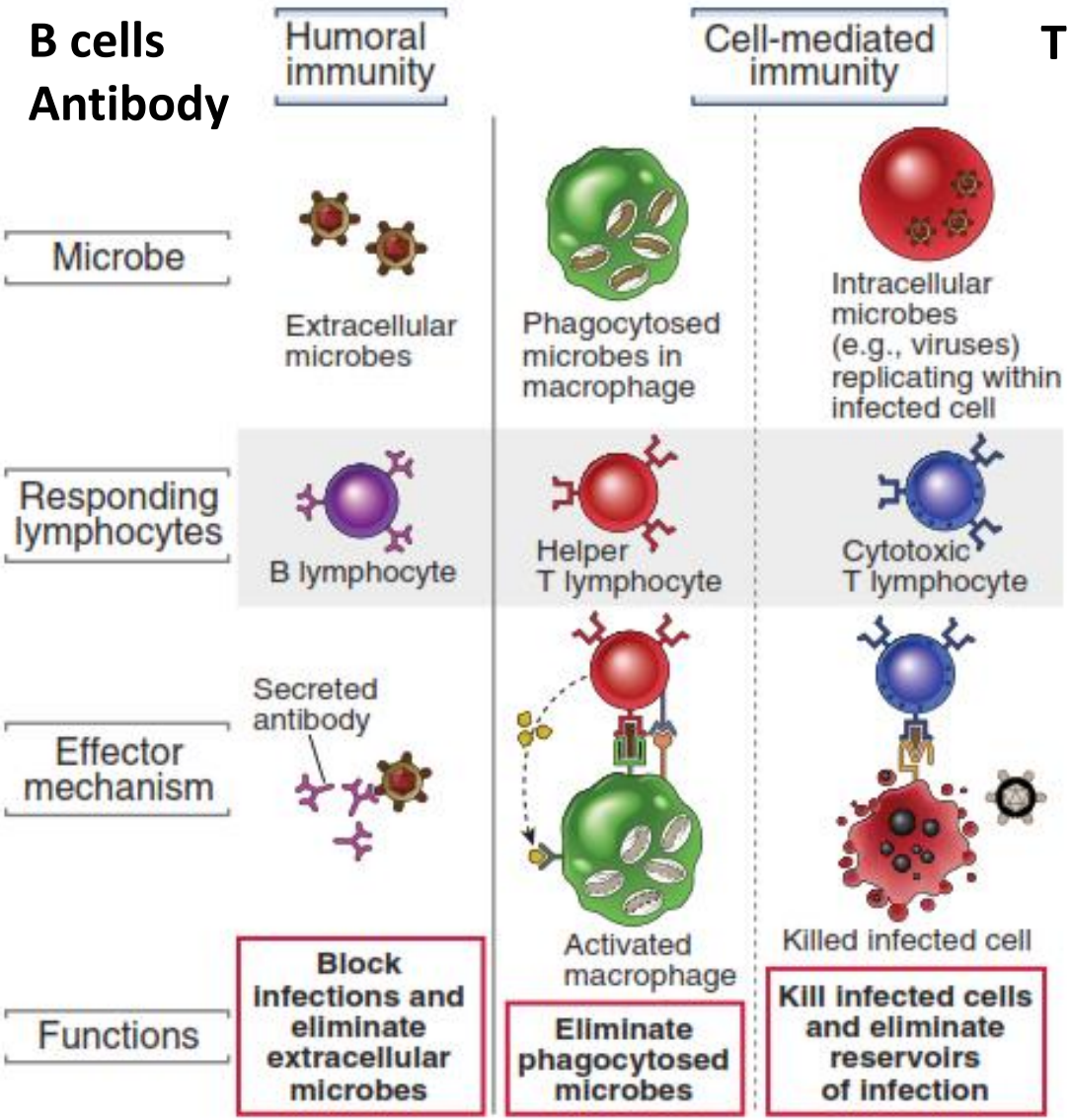
- Circular dsDNA with gap
- ORF S
- ORF P
- ORF C
- ORF X – protein X not in the virion
- Not directly cytopathic

Hepatitis B Virus – Outcome of infection in adults



Two types of adaptive Immunity

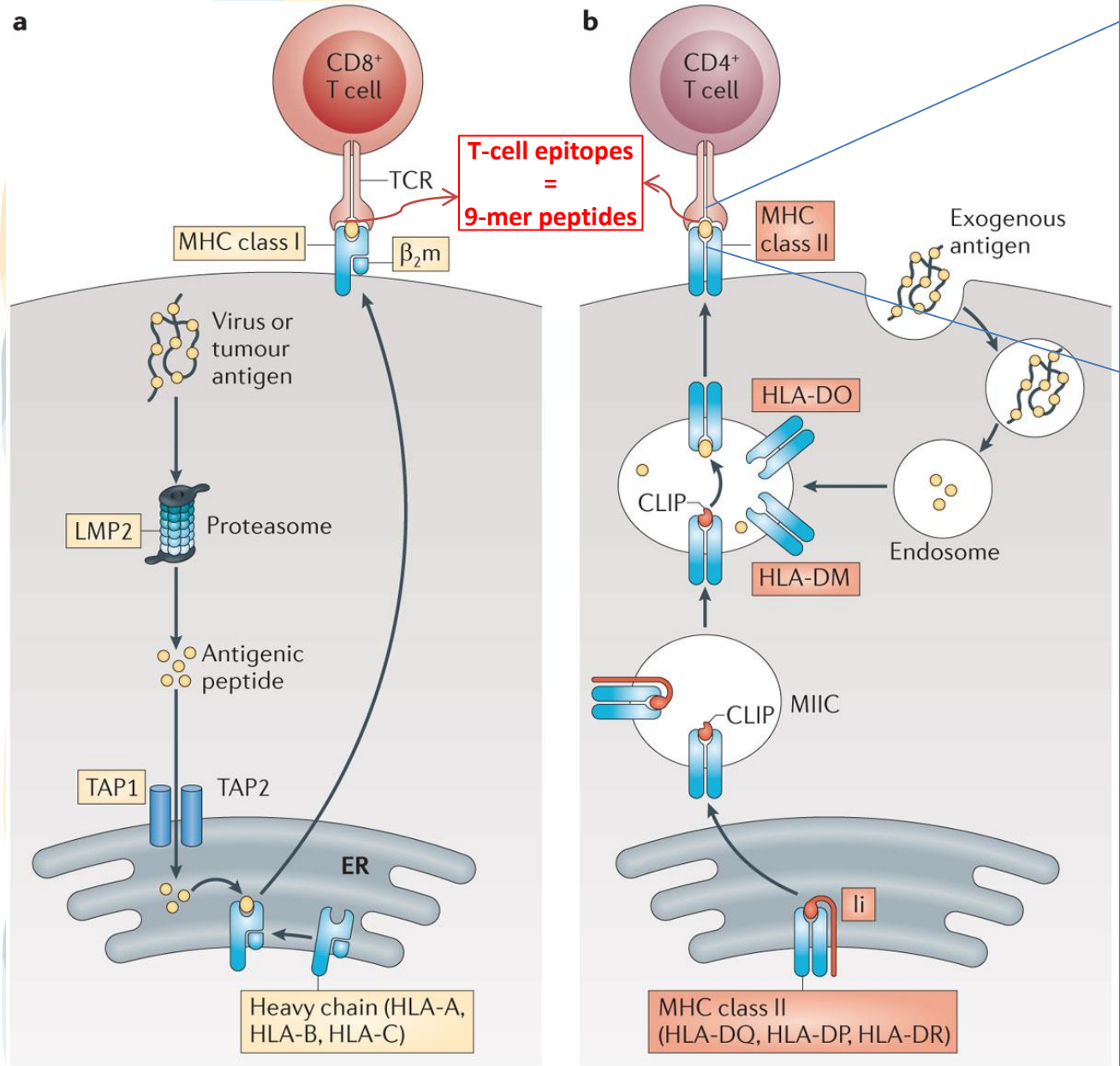
B cells
Antibody

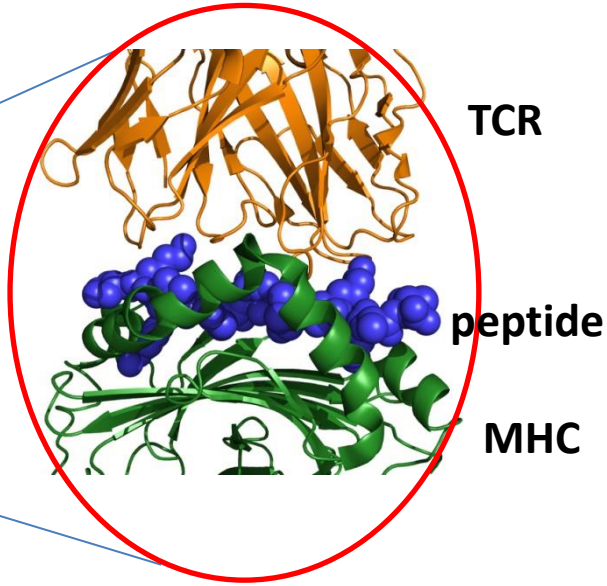


T cells

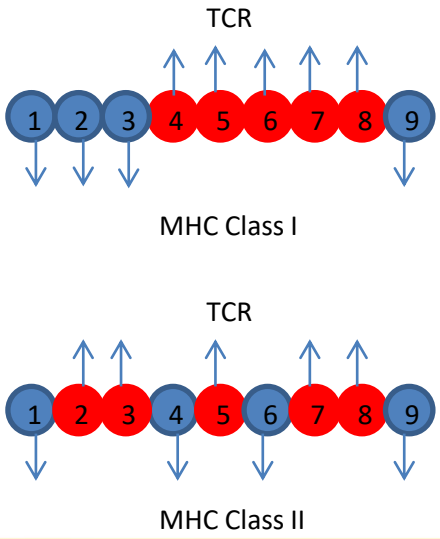
- CD8+ T cells – cytotoxic T cells – kill virus-infected cells, remove virus reservoir.
- CD4+ T cell – Helper T cells – Help B cells to differentiate into antibody secreting plasma cell.
- T cells make contact with virus – infected cells using the T cell receptor which interact with the **peptide** presented by **MHC** (pMHC) on the surface of the infected cells.

Antigen processing inside the cells



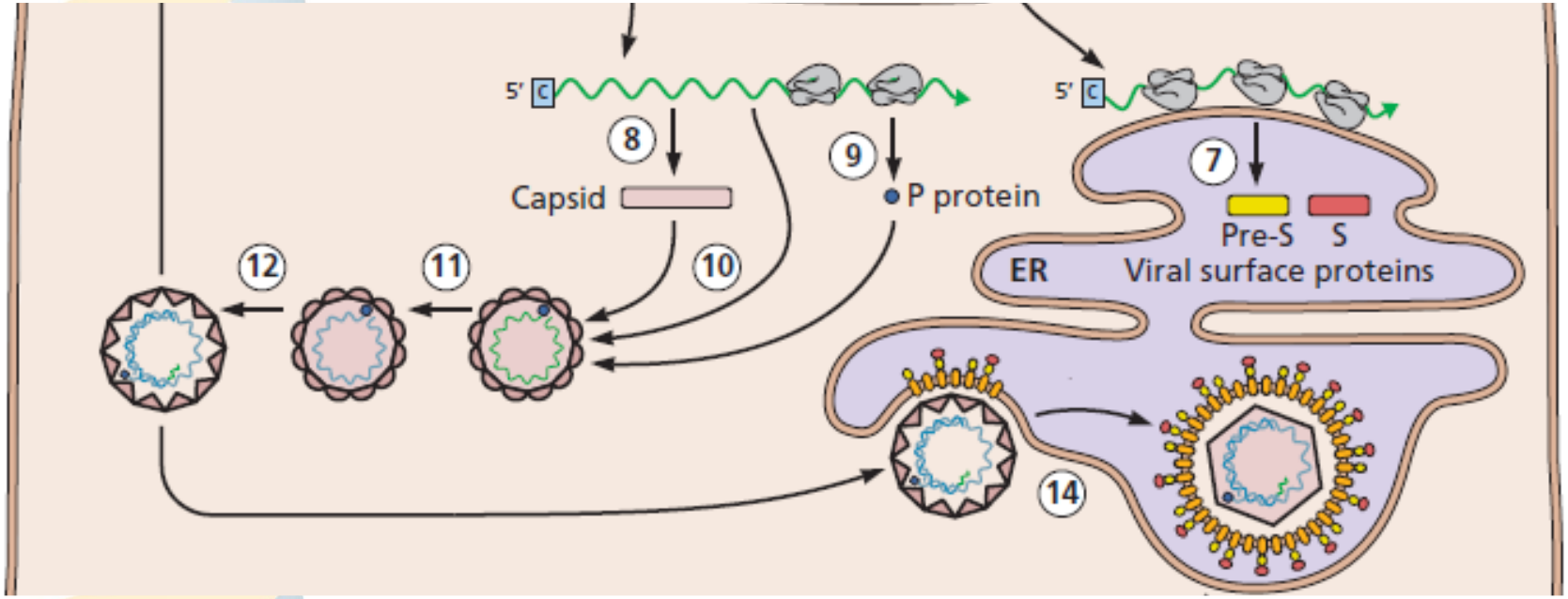


2 faces of T-cell epitope



CLIP : class II-associated invariant chain peptide Ii: MHC class II-associated invariant chain

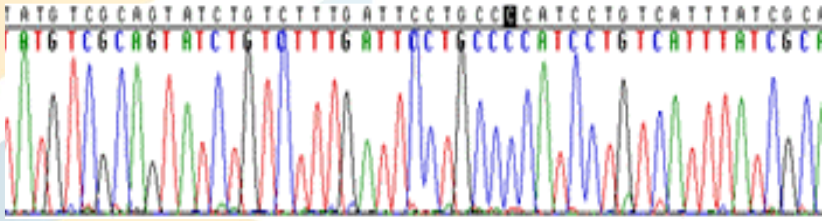
Which viral protein is the ideal target for T cell-based vaccine?



- Pregenome RNA is translated to produce **capsid** and **polymerase** (300: 1) in the cytosol.
- Shorter transcript is translated into viral **surface** protein in the endoplasmic reticulum.
- **Protein X**

“Genome-to-vaccine” approach for HBV

Genome Sequence



Protein Sequence

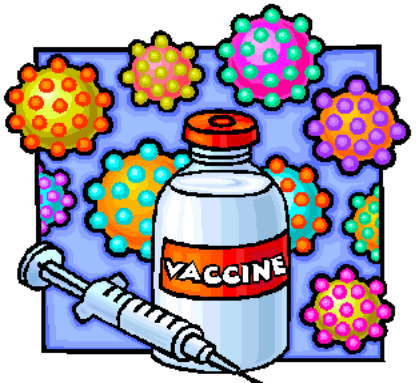
MASQGTKRSYEQMETGGERQNATEIRASVGRMVSGIGRFYIQMCTELKLSDYEGRLIQNSITIERMVLSA
FDERRNRYLEEHPSAGKDPKKTGGPIYRRRDGKWVRELILYDKEEIRRIWRQANNGEDATAGLTHLMIW
HSNLNDATYQRTRALVRTGMDPRMCSLMQGSTLPRRSGAAGAAVKGIGTMVMELIRMIKRGINDRNF
WRGENGRRTRIAYERMCNILKGKFQTAAQRAMMDQVRESRNPGNAEIEDLIFLARSALILRGSVAHKSC
LPACVYGLAVASGYDFEREGYSLVGIDPFRLLQNSQVFSLIRPNENPAHKSQLVWMACHSAAFEDLRVSS
FIRGTRVVPRGQLSTRGVQIASNENMEVMDSNTLELRSRYWAIRTRSGGNTNQQKASAGQISVQPTFSV
QRNLPFERATIMAAFTGNTEGRTSDMRTEIIRMMESARPEDVSFQGRGVFELSDEKATNPIVPSFDMNN
EGSYFFGDNAEEYDN

immunoinformatics analysis

Putative T cell epitopes

+ Antigen delivery system

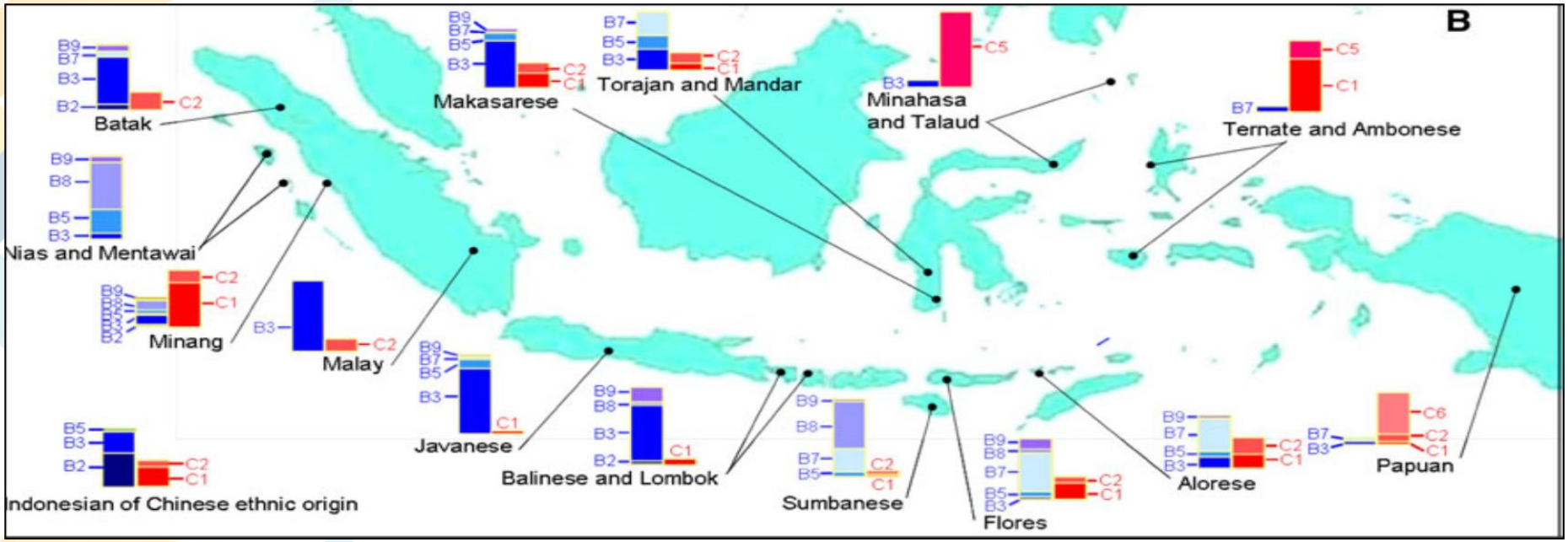
Vaccine candidates



Prototype

Therapeutic vaccine that induces cellular mediated immunity needs to be based on the epitopes derived from the prevalent viral strain and restricted by the prevalent HLA types in the related population.

Distribution of HBV genotypes and subgenotypes in the Indonesian archipelago



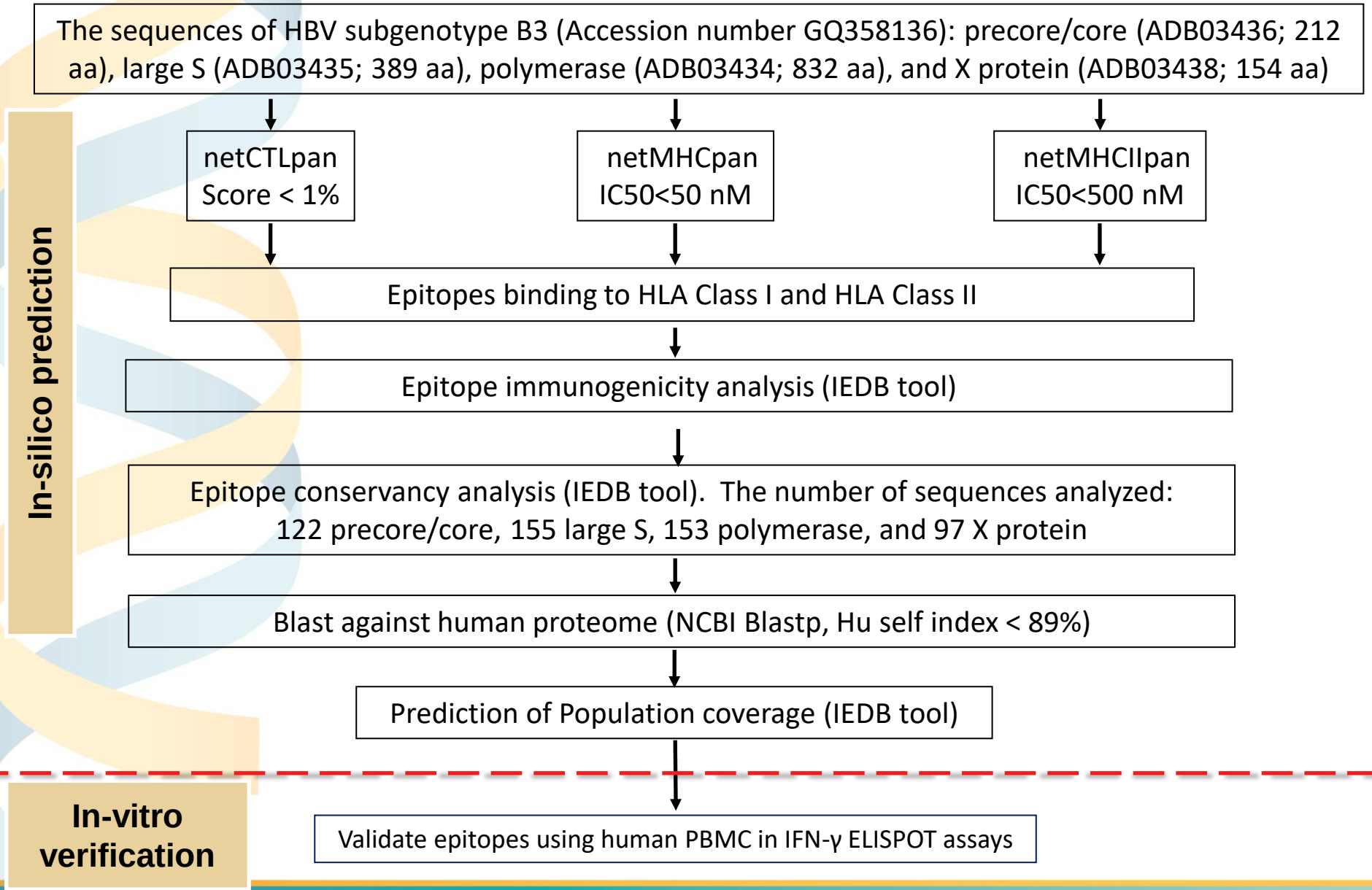
HBV genotype B subgenotype B3 is the most prevalence virus affecting Indonesian people, notably in the western part of Indonesia.

HLA allelotypes and the frequency in Indonesian population

HLA	Allele	Frequency %	HBV T cell epitopes in IEDB
HLA Class I	A*24:07	21,52	1
	A*11:01	16,03	73
	A*33:03	15,61	6
	A*24:02	14,35	82
	B*15:02	11,60	0
	B*15:13	11,20	0
HLA Class II	DRB1*12:02	37,80	3
	DRB1*15:02	23,00	0
	DRB1*07:01	13,10	36

Yuliwulandari et al.,2009 Tissue antigen 73, 46-53

Workflow of epitope identification



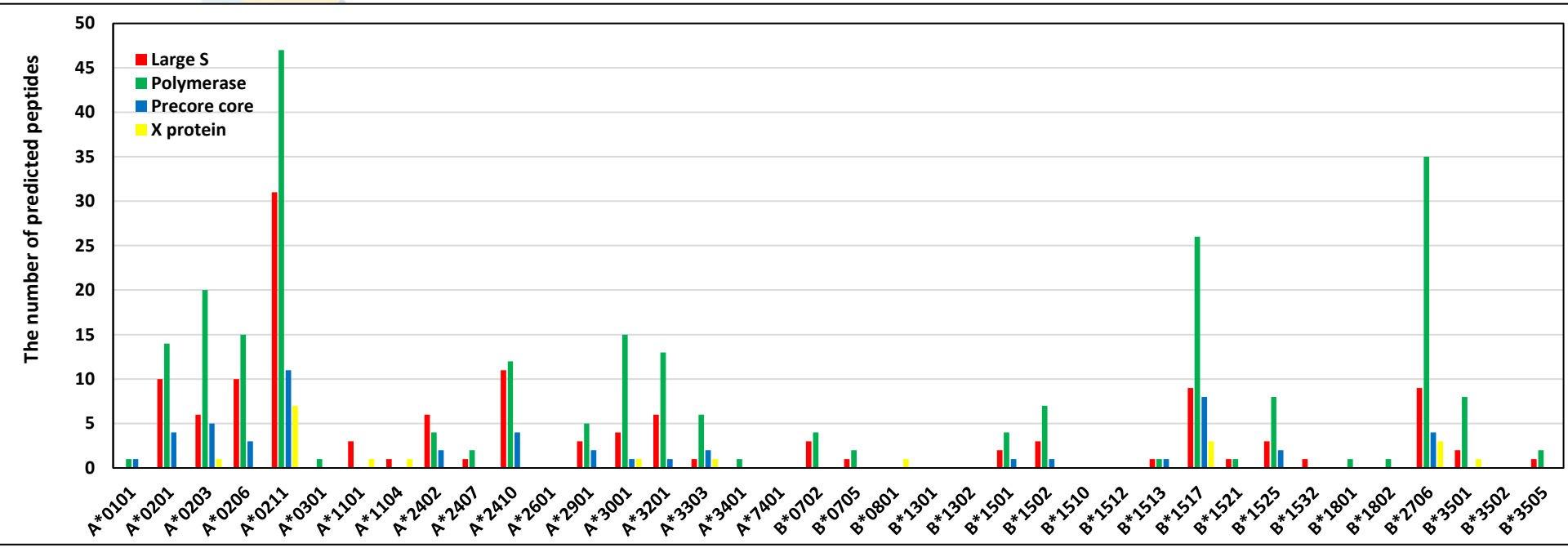
The distribution of T cell epitopes across HBV proteome

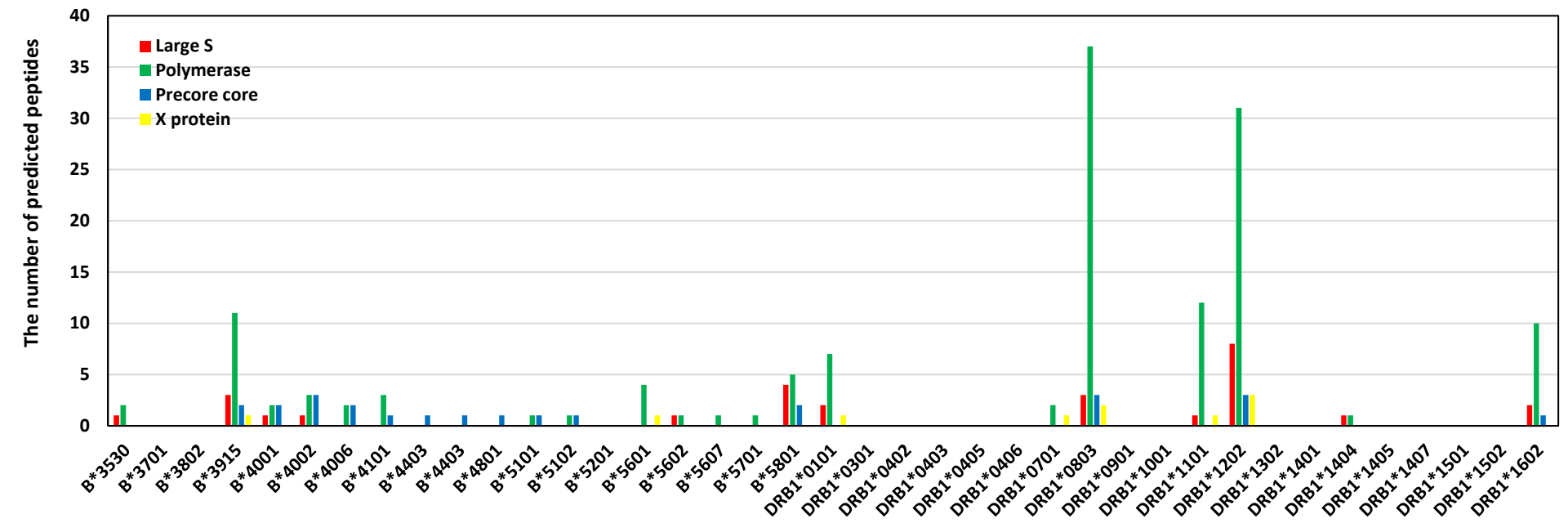
- https://services.healthtech.dtu.dk/service.php?NetCTLpan-1.1 netCTLpan 1% rank
- https://services.healthtech.dtu.dk/service.php?NetMHCpan-4.1 netMHCpan IC50 50 nM
- https://services.healthtech.dtu.dk/service.php?NetMHCIIpan-4.0 netMHCIIpan IC50 500 nM

Proteins	Length	Possible number of nonamer peptides	Predicted epitopes	
			Number	Percentage
Precore/core	212	204	77	37,75 %
Protein X	154	146	30	20,55 %
Polymerase	832	824	393	47,69 %
Large S	389	381	157	41,21 %
TOTAL		1.555	657	

- Screen for immunogenicity
- Epitope conservancy
- Non-similarity to human peptides

The distribution of predicted HBV epitopes across HLA alleles





Benchmark for immunogenicity scale

http://tools.iedb.org/immunogenicity/

Peptide	Length	Score	Source of peptide	
GILGFVFTL	9	0.30484	Influenza matrix protein	Highly immunogenic
FLPSDFFPS	9	0.05405	HBV Core antigen	
FLPSDFFPS	9	0.05405	HBV Core antigen	Immunogenic
YRVVSVLTV	9	-0.05398	Treg epitopes from IgG	
RLSCAASGF	9	-0.15284	Treg epitopes from IgG	
RLSCAASGF	9	-0.15284	Treg epitopes from IgG	
YSLSSVVTV	9	-0.23479	Treg epitopes from IgG	
LQSSGLYSL	9	-0.29739	Treg epitopes from IgG	
LQSSGLYSL	9	-0.29739	Treg epitopes from IgG	
KVSCKASGY	9	-0.40094	Treg epitopes from IgG	
AVLQSSGLY	9	-0.41487	Treg epitopes from IgG	
GLYSLSSVV	9	-0.4497	Treg epitopes from IgG	

Non-immunogenic

Epitopes with negative immunogenicity were removed from the list

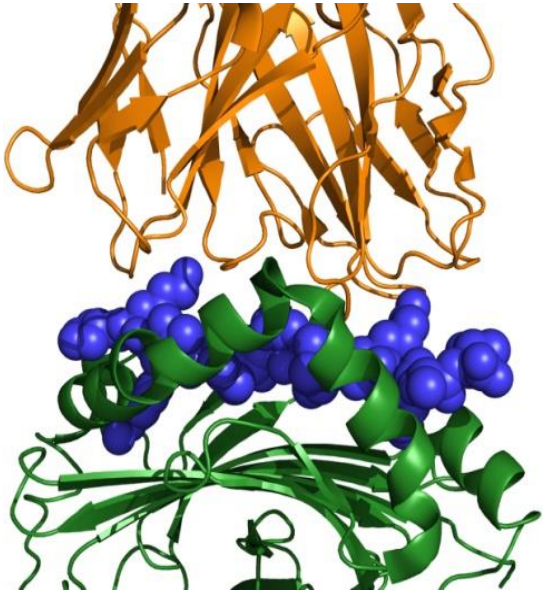
Epitope conservancy analysis

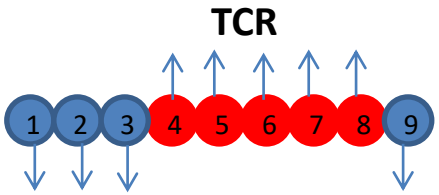
http://tools.iedb.org/conservancy/

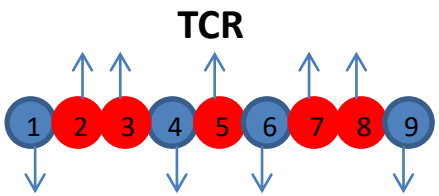
#Pos	Variant	% Cons
007-015	KEFGASVEL	94.19%
	KEFGASVEV	3.49%
	KEFGATVEL	2.33%
010-018	GASVELLSF	94.19%
	GASVEVLSF	3.49%
	GATVELLSF	2.33%
016-024	LSFLPSDFF	95.35%
	LSFLPSDSF	4.65%
052-060	HTALRQAIL	84.88%
	HTALRQAVL	12.79%
	HTALRKAIL	1.16%
	HTALRQAIV	1.16%
063-071	GELMNLATW	94.19%
	GELMTLATW	4.65%
	GDLMTLATW	1.16%
064-072	ELMNLATWV	90.70%
	ELMTLATWV	4.65%
	ELMNLATWL	3.49%
	DLMTLATWV	1.16%

Epitopes variability - consequences for immune recognition:

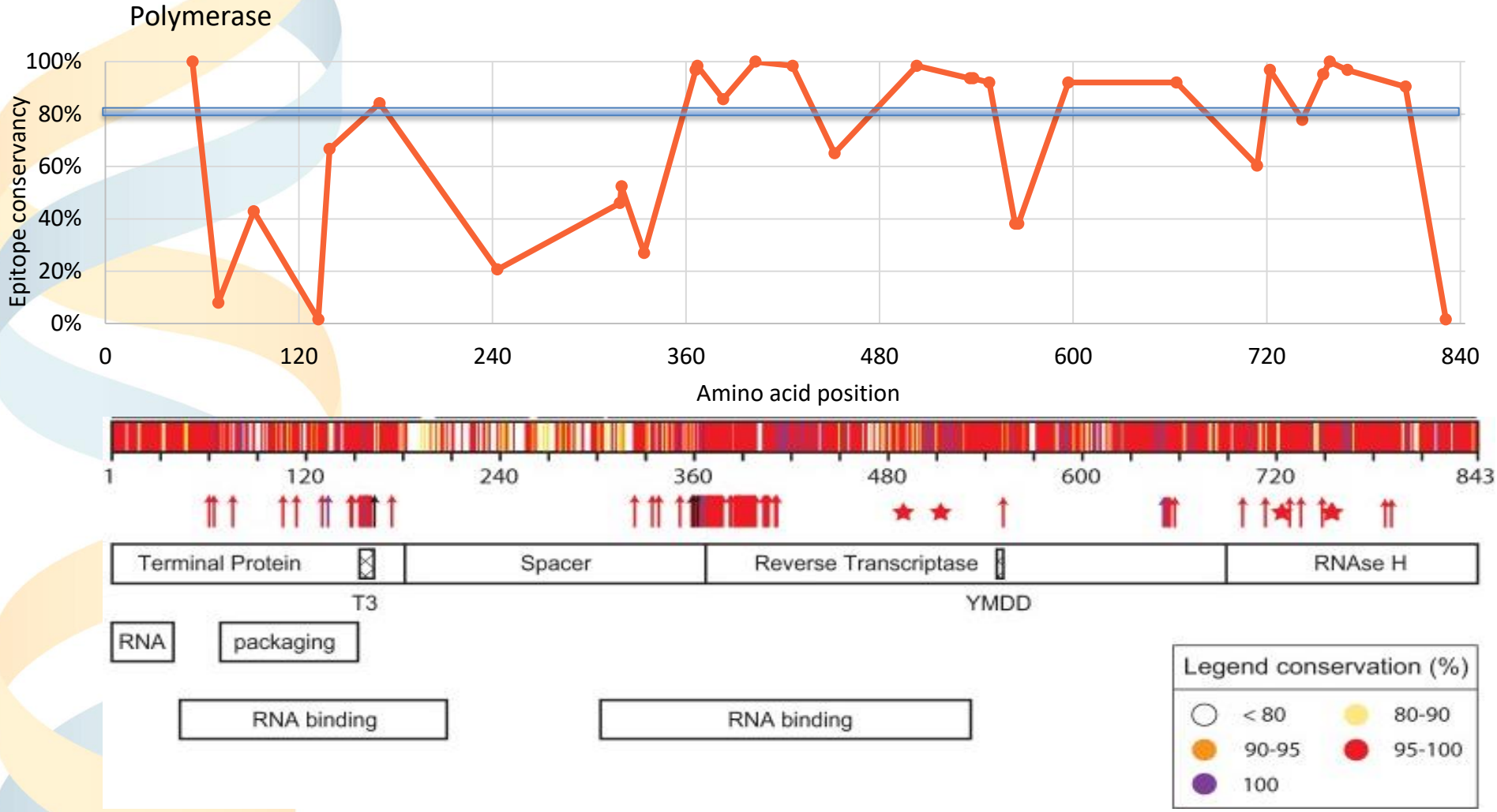
- escape TCR detection
- escape presentation by MHC







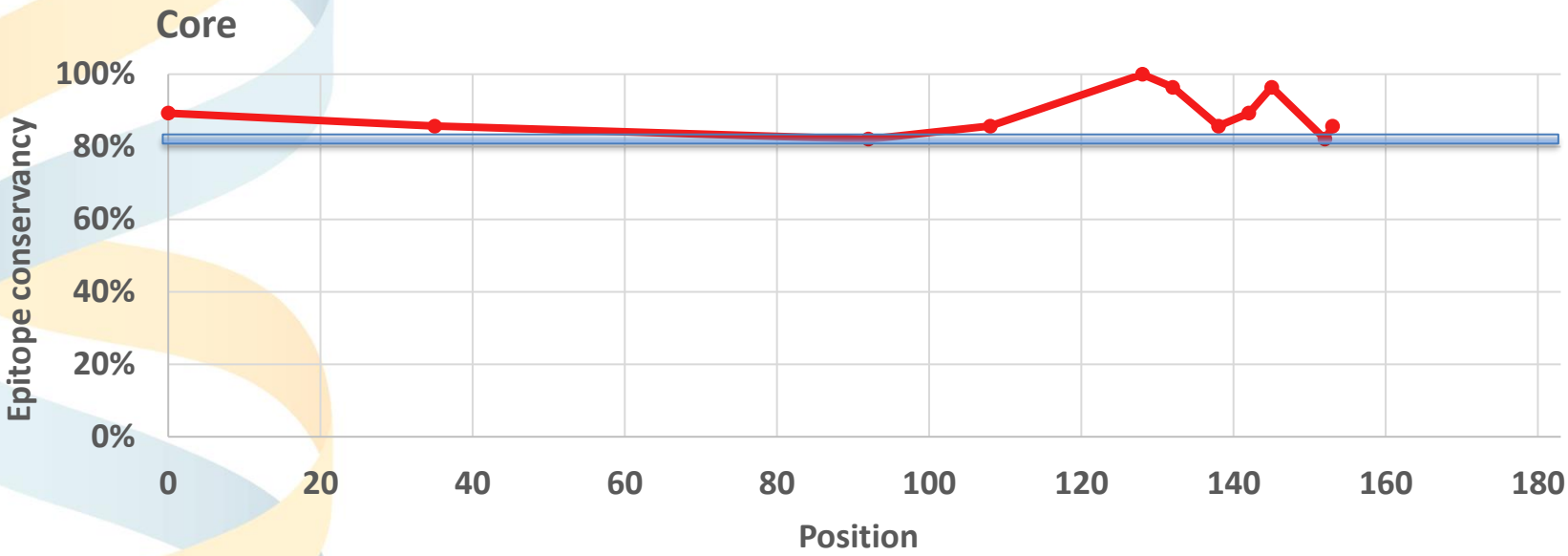
Epitope conservancy analysis

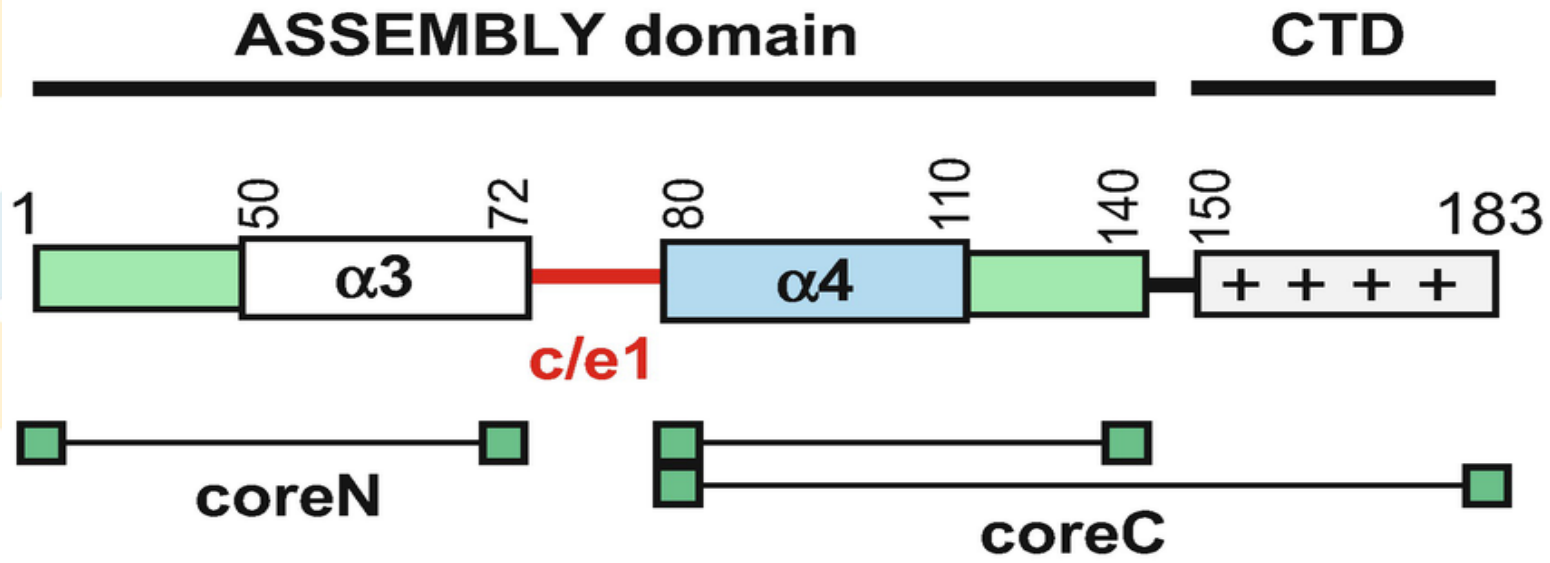


- Target the epitope located at the region that is important for function
- Mutation is unlikely

de Beijer et al., (2020) *Journal of virology*, *94*(7), e01663-19. https://doi.org/10.1128/JVI.01663-19

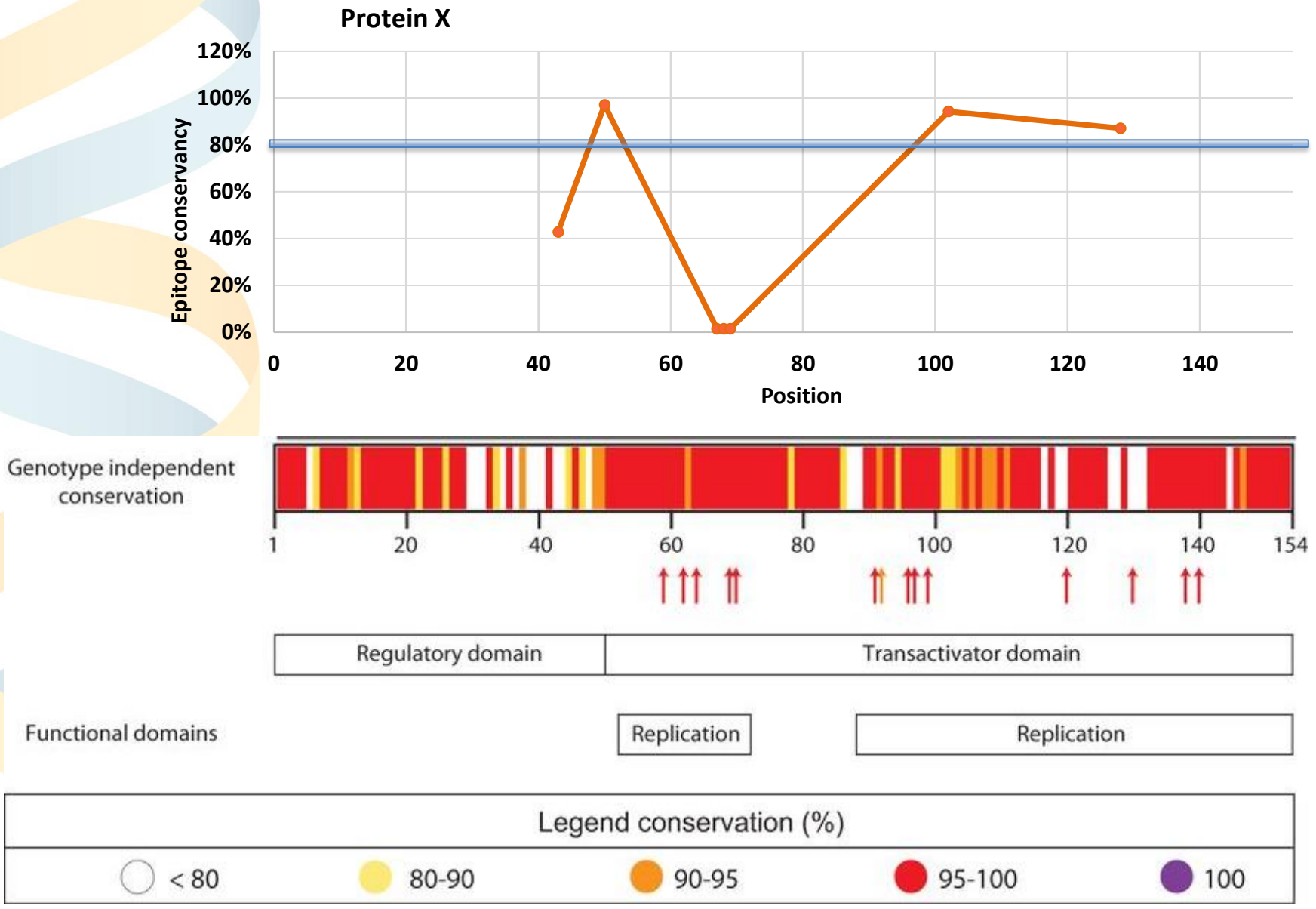
Epitope conservancy analysis



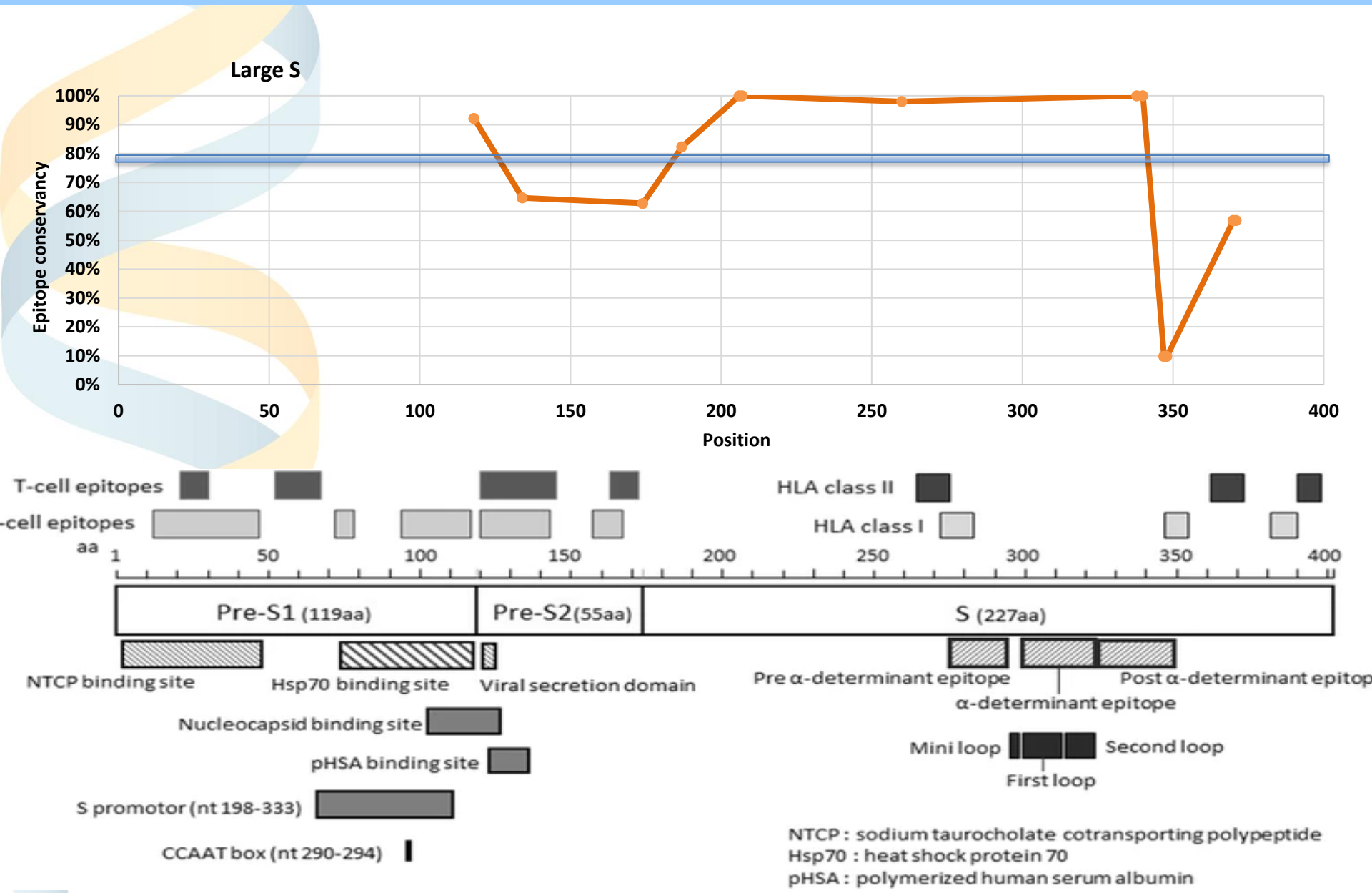


Heger-Stevic et al. (2018) Methods in Molecular Biology, vol 1776. Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-7808-3_33

Epitope conservancy analysis



Epitope conservancy analysis



Hatazawa, et al., *Infect Agents Cancer* **13,** 7 (2018). https://doi.org/10.1186/s13027-018-0179-4

Cross-reactivity with the human proteome

HBV protein	Pos	HBV peptide	Human protein	Human peptide
largeS	260	LL**LCLIFLL**	HHIP-like protein 2 precursor (NP_079022.2; AAH07638.1)	LCLIFLL
largeS	340	SV**RFSWLSL**	ubiquitin-conjugating enzyme E2 J2 isoform 1 (NP_919296.1)	RFSWLSL
polymerase	366	**ARVTGGV**F**L**	immunoglobulin heavy chain junction region(MCC48762.1)	ARVTGGVLL
polymerase	367	RV**TGGVFLV**	solute carrier family 14 (urea transporter), member 2, isoform CRA_b (ID: EAX01455.1)	TGGVFLV
polymerase	664	**QAFTFSP**TY	mitogen activated protein kinase 7 transcript variant 5(AAS38577.1; BAD92848.1)	QAFTFSP
polymerase	806	RP**TTGRTSL**	protein ECT2 isoform c(NP_001336023.1)	TTGRTSL
precorecore	138	FG**RETVLEY**	immunoglobulin heavy chain junction region (MBB1955610.1)	RETVLEY
precorecore	152	**VWIRTPPA**Y	Structure of HLA-A2 P130 (5E00_C)	VWIRTPPA
precorecore	152	**VWIRTPP**AY	hCG2041829, partial (EAW57787.1)	VWIRTPP
Xprotein	102	**STTDLEA**YF	Alanyl-tRNA synthetase 2 (AAI31729.1); AARS2 protein (AAH33169.1)	STTDLEA
Xprotein	050	**HLSLRGL**PV	FLJ00276 protein(BAC85129.1)	HLSLRGL

- Human-like sequences in the vaccine might abrogate proper immune response:
  - Autoimmunity
  - Vaccine not immunogenic.
- Need to be removed from the vaccine components

The distribution of T cell epitopes across HBV proteome

Proteins	Length	Possible number of nonamer peptides	Predicted epitopes	
			Number	Percentage
Precore/core	212	204	77	37,75 %
Protein X	154	146	30	20,55 %
Polymerase	832	824	393	47,69 %
Large S	389	381	157	41,21 %
TOTAL		1.555	657	

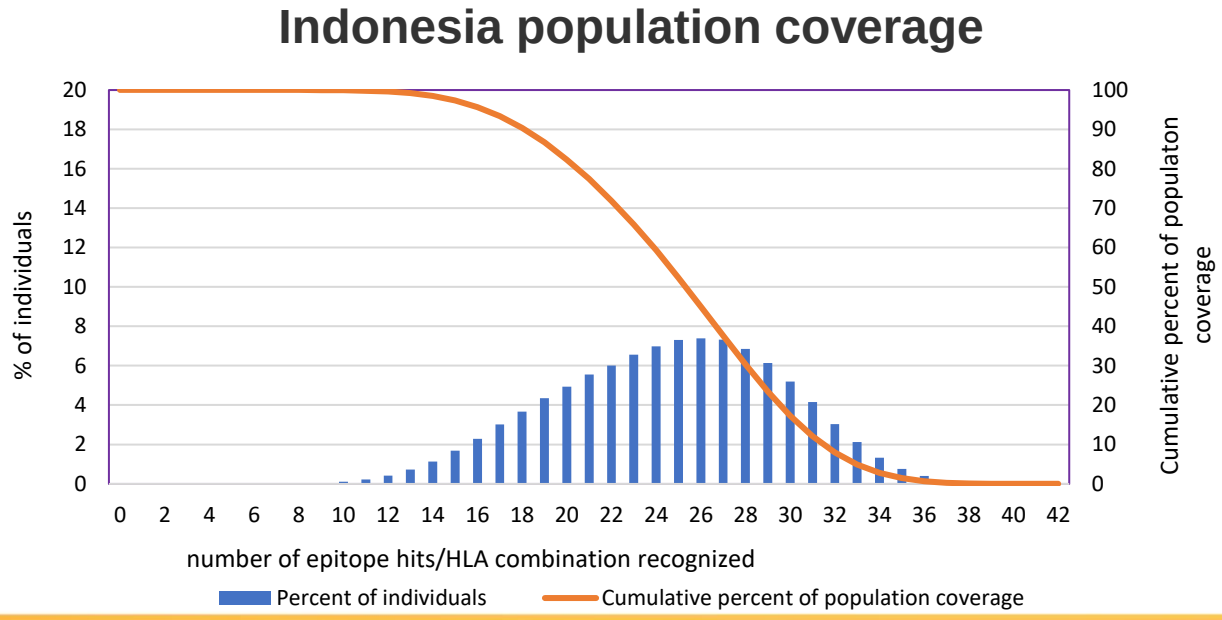
- Promiscuous peptides
- Immunogenic
- Conserve
- Human self index < 7/9

Proteins	Predicted epitopes after screening	
	Number	Percentage
Precore/core	9	4,41 %
Protein X	3	2,05 %
Polymerase	14	1,70 %
Large S	5	1,31 %
TOTAL	31	

Population coverage of the epitopes

population/area	Class combined		
	coverage[a]	average_hit[b]	pc90[c]
Indonesia	100.0%	24.53	18.09
Malaysia	100.0%	22.97	16.32
Malaysia Oriental	100.0%	23.43	17.02
Papua New Guinea	100.0%	18.39	12.33
Philippines	100.0%	23.71	18.09
Singapore	100.0%	20.24	13.9
Southeast Asia	99.98%	17.91	11.15
Thailand	99.98%	18.49	12.03
Vietnam	100.0%	20.03	13.51
Average	99.83	19.54	13.59
Standard deviation	0.43	4.96	4.32

[a] projected population coverage
[b] average number of epitope hits / HLA combinations recognized by the population
[c] minimum number of epitope hits / HLA combinations recognized by 90% of the population



List of predicted HBV epitopes – Large S

No	Protein	Pos	Peptide	HLA alleles	% cons	Immun	%PopCov
1	largeS	118	AMQWNSTTF	HLA-A*24:02; HLA-A*24:07; HLA-A*24:10; HLA-A*32:01; HLA-B*15:01; HLA-B*15:02; HLA-B*15:12; HLA-B*15:21; HLA-B*15:25; HLA-B*15:32	92.16	0.0787	76.99
2	largeS	187	VLQAGFFLL	HLA-A*02:01; HLA-A*02:06; HLA-A*02:11 ;HLA-DRB1*1202	82.35	0.23729	65.85
3	largeS	206	DSWWTSLNF	HLA-B*15:13; HLA-B*15:17; HLA-B*35:01	100.00	0.16372	23.49
4	largeS	207	SWWTSLNFL	HLA-A*24:02; HLA-A*24:07; HLA-A*24:10 ;HLA-DRB1*0405	100.00	0.00236	62.25
5	largeS	338	WASVRFSWL	HLA-B*08:01 ;HLA-DRB1*0701;HLA-DRB1*0901;HLA-DRB1*1502;HLA-DRB1*1602	100.00	0.13824	62.47

List of predicted HBV epitopes - Polymerase

No	Protein	Pos	Peptide	HLA alleles	% cons	Immun	% PopCov
1	Polymerase	54	KVGNFTGLY	HLA-A*01:01; HLA-A*03:01; HLA-A*11:01; HLA-A*11:04; HLA-A*29:01; HLA-A*32:01; HLA-A*74:01; HLA-B*15:17	100.00	0.17715	41.82
2	Polymerase	170	SPYSWEQEL	HLA-B*07:02; HLA-B*07:05; HLA-B*15:10; HLA-B*35:02; HLA-B*35:05; HLA-B*35:30; HLA-B*39:15; HLA-B*51:01; HLA-B*51:02; HLA-B*56:01; HLA-B*56:02; HLA-B*56:07	84.13	0.10302	37.48
3	Polymerase	383	TESRLVVDF	HLA-B*18:01; HLA-B*18:02; HLA-B*40:01; HLA-B*40:02; HLA-B*44:03	85.71	0.07424	37.16
4	Polymerase	403	WPKFAVPNL	HLA-B*07:02; HLA-B*07:05; HLA-B*51:01; HLA-B*51:02; HLA-B*56:02	100.00	0.11162	20.64
5	Polymerase	426	SLDVSAAFY	HLA-A*01:01; HLA-A*29:01 ; HLA-DRB1*0901	98.41	0.02589	10.63
6	Polymerase	503	YSHPIILGF	HLA-A*26:01; HLA-A*32:01; HLA-B*15:13; HLA-B*15:17; HLA-B*57:01; HLA-B*58:01 ; HLA-DRB1*0901	98.41	0.26466	38.96
7	Polymerase	536	VRRAFPHCL	HLA-B*27:06 ; HLA-DRB1*0101; HLA-DRB1*0301; HLA-DRB1*0402; HLA-DRB1*0701; HLA-DRB1*0803; HLA-DRB1*0901; HLA-DRB1*1001; HLA-DRB1*1101; HLA-DRB1*1202; HLA-DRB1*1302; HLA-DRB1*1401; HLA-DRB1*1404; HLA-DRB1*1405; HLA-DRB1*1407; HLA-DRB1*1501; HLA-DRB1*1502; HLA-DRB1*1602	93.65	0.15553	99.24
8	Polymerase	538	RAFPHCLAF	HLA-A*24:07; HLA-A*24:10; HLA-A*32:01; HLA-B*07:02; HLA-B*07:05; HLA-B*13:01; HLA-B*13:02; HLA-B*15:01; HLA-B*15:02; HLA-B*15:10; HLA-B*15:12; HLA-B*15:13; HLA-B*15:17; HLA-B*15:21; HLA-B*15:25; HLA-B*15:32; HLA-B*27:06; HLA-B*35:01; HLA-B*35:02; HLA-B*35:05; HLA-B*35:30; HLA-B*39:15; HLA-B*48:01; HLA-B*52:01; HLA-B*56:02; HLA-B*57:01; HLA-B*58:01	93.65	0.02109	91.86
9	Polymerase	548	YMDDVVLGA	HLA-A*02:01; HLA-A*02:03; HLA-A*02:06; HLA-A*02:11 ; HLA-DRB1*0301; HLA-DRB1*0402; HLA-DRB1*0403; HLA-DRB1*0405; HLA-DRB1*0406; HLA-DRB1*0701; HLA-DRB1*0901; HLA-DRB1*1001; HLA-DRB1*1302; HLA-DRB1*1407; HLA-DRB1*1502	92.06	0.11902	78.08
10	Polymerase	597	YVIGSWGTL	HLA-A*26:01; HLA-A*34:01; HLA-B*56:02 ; HLA-DRB1*0101; HLA-DRB1*0901; HLA-DRB1*1502	92.06	0.17599	54.83
11	Polymerase	722	LPIHTAELL	HLA-B*07:02; HLA-B*07:05; HLA-B*35:01; HLA-B*35:02; HLA-B*35:05; HLA-B*35:30; HLA-B*39:15; HLA-B*51:01; HLA-B*51:02; HLA-B*56:01; HLA-B*56:02; HLA-B*56:07 ; HLA-DRB1*0701	96.83	0.2284	50.56
12	Polymerase	755	KYTSFPWLL	HLA-A*24:02; HLA-A*24:07; HLA-A*24:10 ; HLA-DRB1*0101; HLA-DRB1*0403; HLA-DRB1*0405; HLA-DRB1*0406; HLA-DRB1*0701; HLA-DRB1*0901; HLA-DRB1*1001; HLA-DRB1*1404; HLA-DRB1*1407; HLA-DRB1*1501; HLA-DRB1*1502; HLA-DRB1*1602	95.24	0.13015	90.55
13	Polymerase	759	FPWLLGCAA	HLA-B*35:01; HLA-B*35:02; HLA-B*35:05; HLA-B*35:30; HLA-B*56:01; HLA-B*56:02; HLA-B*56:07 ; HLA-DRB1*0101	100.00	0.0592	22.29
14	Polymerase	770	ILRGTSFVY	HLA-A*03:01; HLA-A*29:01; HLA-B*15:01; HLA-B*15:02; HLA-B*15:12; HLA-B*15:13; HLA-B*15:21; HLA-B*15:25; HLA-B*15:32; HLA-B*35:05; HLA-B*35:30 ; HLA-DRB1*0101; HLA-DRB1*0301; HLA-DRB1*0402; HLA-DRB1*0403; HLA-DRB1*0405; HLA-DRB1*0406; HLA-DRB1*0701; HLA-DRB1*0901; HLA-DRB1*1001; HLA-DRB1*1202; HLA-DRB1*1302; HLA-DRB1*1401; HLA-DRB1*1404; HLA-DRB1*1405; HLA-DRB1*1407; HLA-DRB1*1501; HLA-	96.83	0.05589	99.57

List of predicted HBV epitopes – Precore/core

No	Protein	Pos	Peptide	HLA alleles	% cons	Immun	% PopCov
1	precorecore	0	MQLFHLCLI	HLA-A*02:06; HLA-B*13:02; HLA-B*37:01; HLA-B*48:01; HLA-B*52:01; HLA-DRB1*1202	89.29	0.08328	62.36
2	precorecore	35	KEFGASVEL	HLA-B*13:01; HLA-B*13:02;HLA-B*15:10;HLA-B*18:01;HLA-B*18:02;HLA-B*37:01;HLA-B*38:02;HLA-B*39:15;HLA-B*40:01;HLA-B*40:02;HLA-B*40:06;HLA-B*41:01;HLA-B*44:03;HLA-B*48:01	85.71	0.04781	51.29
3	precorecore	92	ELMNLATWV	HLA-A*02:03; HLA-A*34:01; HLA-DRB1*0402	82.14	0.1247	21.65
4	precorecore	108	ASRELVVSY	HLA-B*15:01;HLA-B*15:02;HLA-B*15:12;HLA-B*15:13;HLA-B*15:17;HLA-B*15:21;HLA-B*15:25;HLA-B*15:32	85.71	0.08379	57.52
5	precorecore	128	LLWFHISCL	HLA-A*02:01;HLA-A*02:11;HLA-B*08:01 ;HLA-DRB1*0405;HLA-DRB1*1501;HLA-DRB1*1502	100.00	0.17536	56.77
6	precorecore	132	HISCLTFGR	HLA-A*33:03;HLA-A*74:01 ;HLA-DRB1*0803;HLA-DRB1*1101;HLA-DRB1*1401;HLA-DRB1*1404;HLA-DRB1*1405;HLA-DRB1*1407;HLA-DRB1*1502;HLA-DRB1*1602	96.43	0.03639	67.54
7	precorecore	142	TVLEYLVSF	HLA-A*02:06;HLA-A*32:01;HLA-B*15:02;HLA-B*15:13;HLA-B*35:01;HLA-B*35:05;HLA-B*35:30	89.29	0.02129	57.28
8	precorecore	145	EYLVSFGVW	HLA-A*24:02,HLA-A*24:07,HLA-A*24:10	96.43	0.03976	60.92
9	precorecore	153	WIRTPPAYR	HLA-A*33:03 ;HLA-DRB1*0101;HLA-DRB1*0301;HLA-DRB1*0403;HLA-DRB1*0405;HLA-DRB1*0406;HLA-DRB1*0701;HLA-DRB1*0803;HLA-DRB1*0901;HLA-DRB1*1001;HLA-DRB1*1101;HLA-DRB1*1202;HLA-DRB1*1302;HLA-DRB1*1401;HLA-DRB1*1404;HLA-DRB1*1405;HLA-DRB1*1407;HLA-DRB1*1501;HLA-DRB1*1502;HLA-DRB1*1602	85.71	0.06548	99.73

List of predicted HBV epitopes – X Protein

No	Protein	Pos	Peptide	HLA alleles	% cons	Immun	% Pop Cov
1	Xprotein	50	HLSLRGLPV	HLA-B*08:01 ;HLA-DRB1*0101;HLA-DRB1*0405;HLA-DRB1*0701;HLA-DRB1*0803;HLA-DRB1*0901;HLA-DRB1*1001;HLA-DRB1*1101;HLA-DRB1*1202;HLA-DRB1*1404;HLA-DRB1*1407;HLA-DRB1*1501;HLA-DRB1*1502;HLA-DRB1*1602	97.14	0.0016	98.42
2	Xprotein	102	STTDLEAYF	HLA-A*26:01; HLA-B*57:01; HLA-B*58:01	94.29	0.14923	15.56
3	Xprotein	128	KVFVLGGCR	HLA-A*74:01 ;HLA-DRB1*0803;HLA-DRB1*1101;HLA-DRB1*1602	87.14	0.09774	12.45

Conclusions

Allele	Frequency %	HBV T cell epitopes in IEDB	HBV T cell epitopes predicted in this study
A*24:07	21,52	1	5
B*15:02	11,60	0	5
B*15:13	11,20	0	6
DRB1*12:02	37,80	3	6
DRB1*15:02	23,00	0	10

Conclusion

- Immunoinformatics analysis help in the design of genome derived epitope-based vaccine and immunotherapeutic for chronic infection like hepatitis B.
- 31 HBV peptides have been identified, promiscuous, conserve, not-similar to human self peptides, and cover 100% of Indonesian population.
- Immunoinformatics analysis guide selection of vaccine components
  - Targeting the region that virus unlikely mutate
  - Avoiding sequence similarity with human peptides
  - Cover targeted population (based on HLA alleles and the prevalence viral genotypes)
- Immunoinformatics combine with in-vitro and ex-vivo immunology assay is a tool to identify target antigen for vaccine, diagnostic, and other immunotherapy-adoptive T cell transfer.

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Thank you