LaSalle Universidad

DIRECCIÓN DE INVESTIGACIÓN

Universidad Católica San Pablo

Principales estrategias y métodos basados en deep learning para la detección de neo antígenos en el marco del desarrollo de vacunas personalizadas en la inmunoterapia del cáncer

Proyecto en colaboración Universidad La Salle y UCSP

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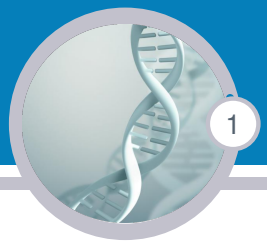
Contenido



Contenido

Proyecto
Financiamiento

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Proyecto
Duración y equipo de trabajo

- Seis (06) meses.
- Equipo:
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  - Valeria Goyzueta (ULaSalle).
  - Yván Tupac (UCSP).
  - Maria Cruz (UCSP).

Inmunoterapia del Cáncer

Es un tipo de tratamiento contra el Cáncer que estimula las defensas naturales del cuerpo para combatir el Cáncer [1].

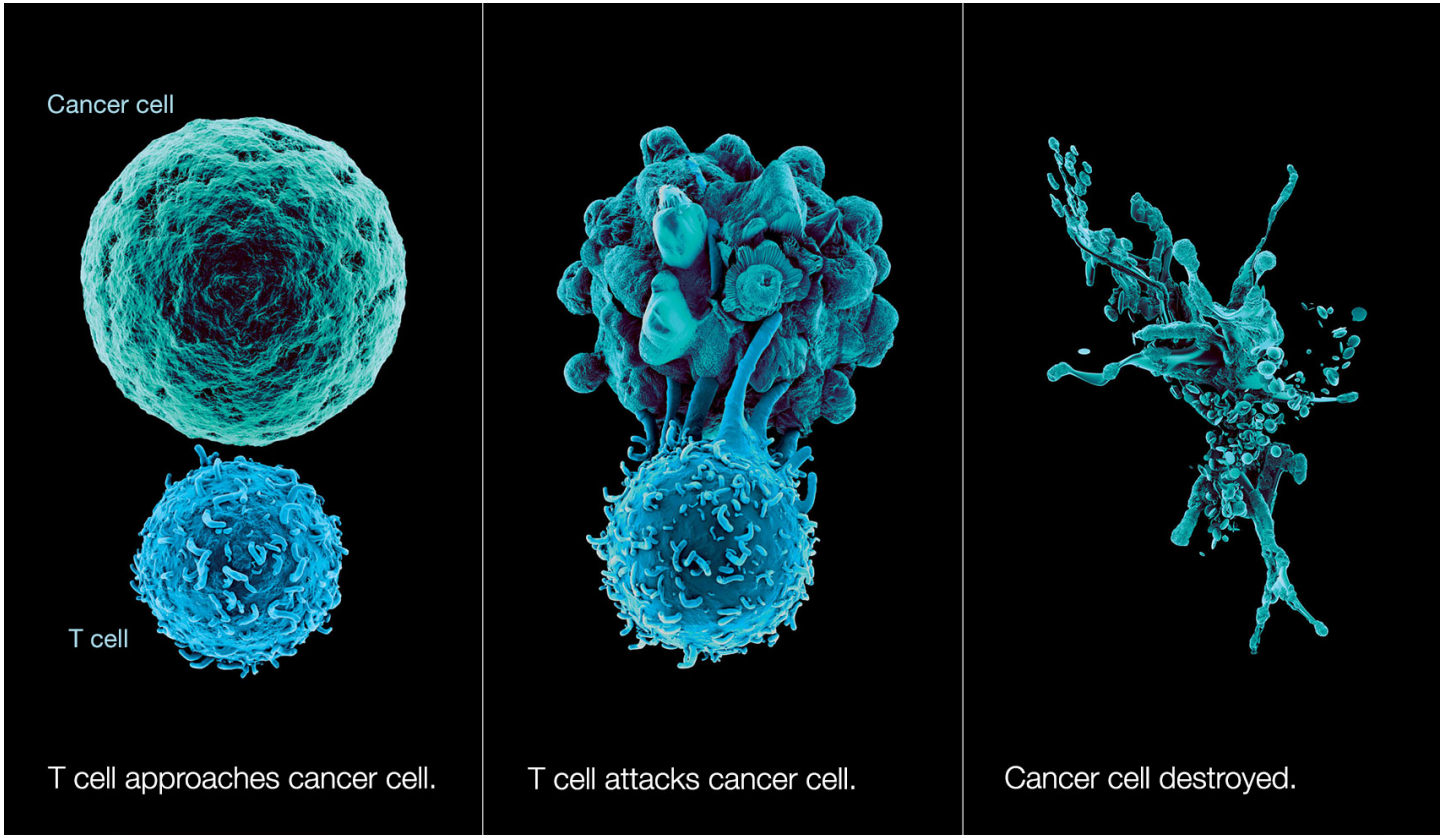


Figure: Ejemplo de como una célula T destruye células del cancer [2].

Inmunoterapia del Cáncer
Neo antígenos

Es una **proteína** que se forma en las células de Cáncer cuando ocurre mutaciones en el DNA, cumplen un rol importante al **estimular una respuesta inmune** [3, 4].

En la actualidad hay varios métodos para detectar a predecir neo antígenos, pero **solo una pequeña cantidad de ellos** logran estimular al sistema inmune [5, 6].

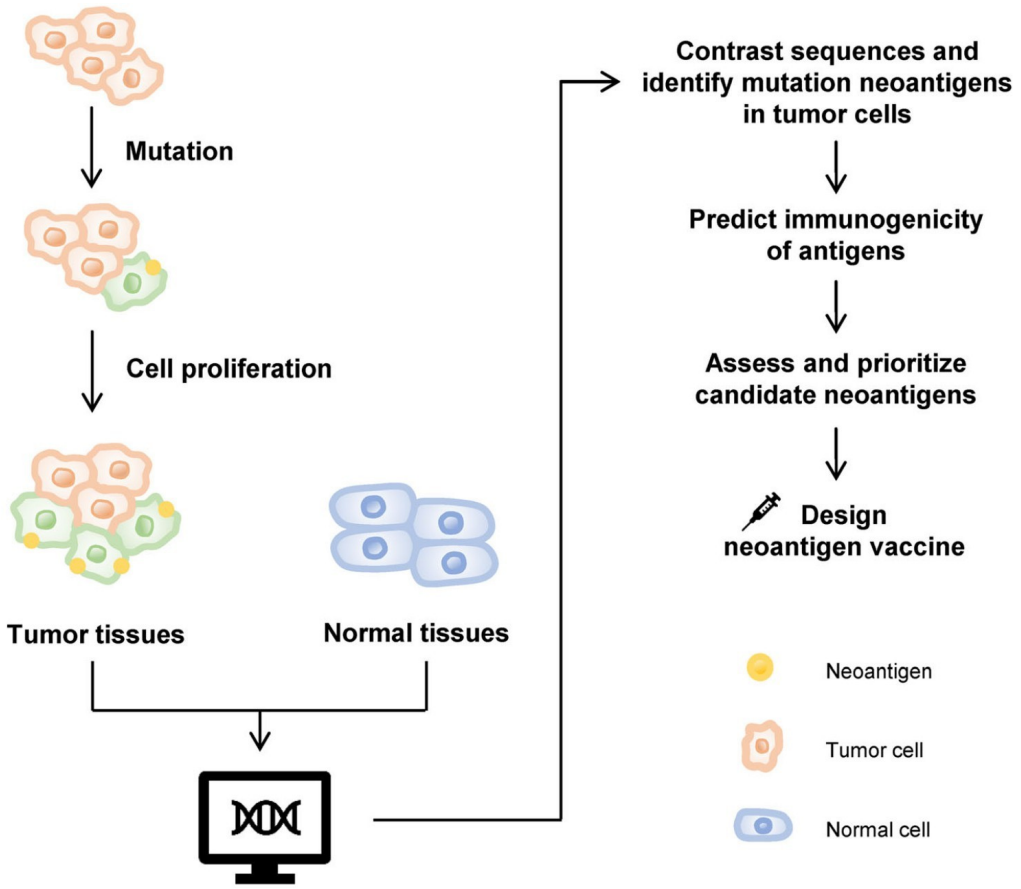


Figure: Proceso para la generación de vacunas personalizadas [7].

MHC-I

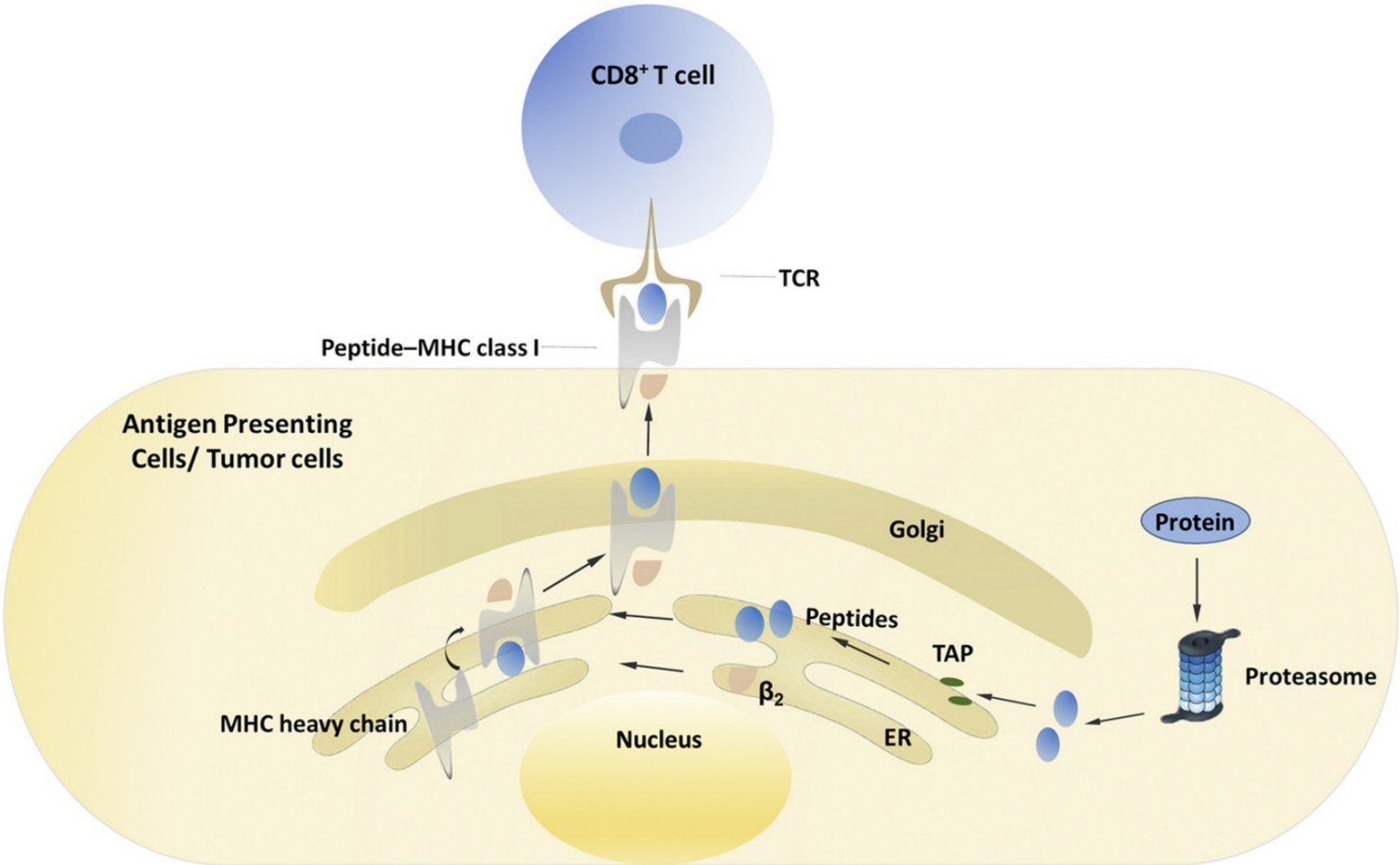


Figure: Presentación de antígenos por MHC-I. Fuente: [8]

Motivación

El cáncer representa el mayor problema de salud mundial, pero lamentablemente los métodos basados en cirugías, radioterapias, quimioterapias tienen baja efectividad [7].

La inmunoterapia del cáncer es una alternativa para el desarrollo de vacunas personalizadas, pero este proceso depende de una correcta detección de neo antígenos [9, 7].

Problema

Menos del 3% de los neoantígenos detectados logran activar a las células T (sistema inmune) [9].

Objetivo general

Desarrollar una revisión sistemática de métodos que utilizan *deep learning* para la detección de neo antígenos.

Contenido

Table: Research questions used in SLR.

Preguntas de investigación
Q1. Como se utilizan las técnicas de *deep learning* para la detección de neo antígenos?
Q2. Que tipos de datos y pre procesamiento es utilizado en la detección de ne antígenos?
Q3. Que bases de datos son utilizadas en la detección de neo antígenos?
Q4. Que método basado en *deep learning* tiene los mejores resultados?

Table: Cadenas de busqueda utilizadas en la RSL.

Cadena de busqueda
neoantigen AND (detection OR pipeline) AND deep learning
(MHC OR HLA) AND binding AND deep learning
(MHC-I OR MHC-II OR MHC OR HLA) AND (peptide OR epitope) AND (binding OR affinity OR prediction OR detection OR presentation)
TCR interaction prediction

Table: Bases de datos utilizadas en la RSL.

Bases de datos
IEEE Xplore
Science Direct
Springer
ACM Digital Library
PubMed
BioRxiv

Table: Criterios de inclusión y exclusión de artículos utilizados en la RSL.

Criterios de inclusión	**Criterios de exclusión**
Artículos con categoría ERA (A, B o C) si son conferencias y Journals Q1, Q2 o Q3.	Trabajos de baja calidad, que no esten rankeados.
Sobre *deep learning*	
La metodología es detallada.	
Tiene repositorio de código fuente y base de datos (deseable).	

Table: Cantidad de artículos encontrados y seleccionados según los criterios de inclusión y exclusión en la RSL.

Año	Artículos encontrados	Artículos seleccionados
2018	57	21
2019	72	31
2020	86	29
2021	61	34
2022	58	19
Total	**334**	**134**

Table: List of research since 2018 that uses CNNs for peptide-MHC binding and presentation.

Year	Ref.	Approach	Name	MHC	Encoding
2022	[10]	pMHC(b)	DeepMHCII	II	PFR
2021	[11]	pMHC(b)	DeepImmuno	I	AAindex1
2021	[12]	pMHC(p)	APPM	I	One-hot
2021	[13]	pMHC(p)	MHCfovea	I	One-hot
2021	[14]	pMHC(b)	CNN-PepPred	II	BLOSUM
2020	[15]	pMHC(b)	IConMHC	I	PCA and AAindex3
2020	[16]	pMHC(b)	OnionMHC	I	BLOSUM and structural features
2020	[17]	pMHC(p)	MINERVA	I	Physicochemical properties
2019	[18]	pMHC(b)	CNN-NF	I	Sequence, Hydropathy, Polarity, Length
2019	[19]	pMHC(b)	DeepSeqPan	I	One-hot
2018	[20]	pMHC(b)	ConvMHC	I	Contact side HLA.peptide

Table: List of research since 2018 that uses CNNs s with RNN or attention mechanisms for peptide-MHC binding and presentation. MHCherryPan uses CNN with RNN, the other uses CNN witn Attention mechanims.

Year	Ref.	Approach	Name	MHC	Encoding
2021	[21]	pMHC(b)	DeepNetBim	I	BLOSUM
2021	[22]	pMHC(b)	Deep Attention Pan	I	BLOSUM
2019	[23]	pMHC(b)	ACME	I	BLOSUM
2020	[24]	pMHC(b)	MHCherryPan	I	BLOSUM

Table: List of research since 2018 that uses RNNs for peptide-MHC binding and presentation. MATHLA, DeepSeqPanII and DeepHLApan uses RNN with attention mechanims, meanwhile the other focus on GRU and LSTM.

Year	Ref.	Approach	Name	MHC	Encoding
2021	[25]	pMHC(b)	MATHLA	I	BLOSUM
2021	[26]	pMHC(b)	DeepSeqPanII	II	One-hot and BLOSUM
2021	[27]	pMHC(b)	GRU-based RNN	II	Embeding layer
2021	[28]	pMHC(b)	BVLSTM-MHC	I	One-hot and BLOSUM
2020	[29]	pMHC(b)	MHCnuggets	I, II	One-hot
2019	[30]	pMHC(b)	DeepHLApan	I	One-hot

Table: List of research since 2018 that uses Transformers (self-attention) for peptide-MHC binding and presentation.

Year	Ref.	Approach	Name	MHC	Encoding
2022	[31]	pMHC(b)	MHCRoBERTa	I	Tokenized from a pre-trained model
2022	[32]	pMHC(b)	TransPHLA	I	Character embedding model
2021	[33]	pMHC(b)	BERTMHC	II	Embeding layer
2021	[34]	pMHC(p)	ImmunoBERT	I	Embeding layer

Table: Public databases of *pMHC binding*, *pMHC presentation*, pMHC-TCR interaction, and 3D structures of proteins.

Name	Year ref.	Description
VDJdb	2018 [35]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [36]	The bigger database, contains information *T-cell epitopes*
TSNAdb	2018 [37]	It contains 7748 samples of mutations and HLA of 16 types of cancer.
NeoPeptide	2019 [38]	It contains samples of neoantigens resulting from somatic mutations and related items. 1818137 epitopes of more than 36000 neoantigens.
pHLA3D	2019 [39]	Presents 106 3D structures of the alpha, *beta2M* chains, and peptides of HLA-I molecules
dbPepNeo	2020 [40]	It has validated samples of the *peptide-MHC* bond, from MS. It contains 407794 low-quality samples, 247 medium-quality, and 295 high-quality samples.
dbPepNeo2.0	2022 [41]	It gathers a list of neoantigens and HLA molecules. It presents 801 high-quality and 842,289 poor-quality HLAs. Also, 55 class II neoantigens and 630 TCR-bound neo antigens.
IntroSpect	2022 [42]	Tool for building databases on *peptide-MHC binding*. It uses data from *Mass Spectrometry*.
IPD-IMGT/HLA	2022 [43]	With 25000 MHC molecules and 45 alleles.

Table: List of *pipelines* since 2018 for the detection of neoantigens.

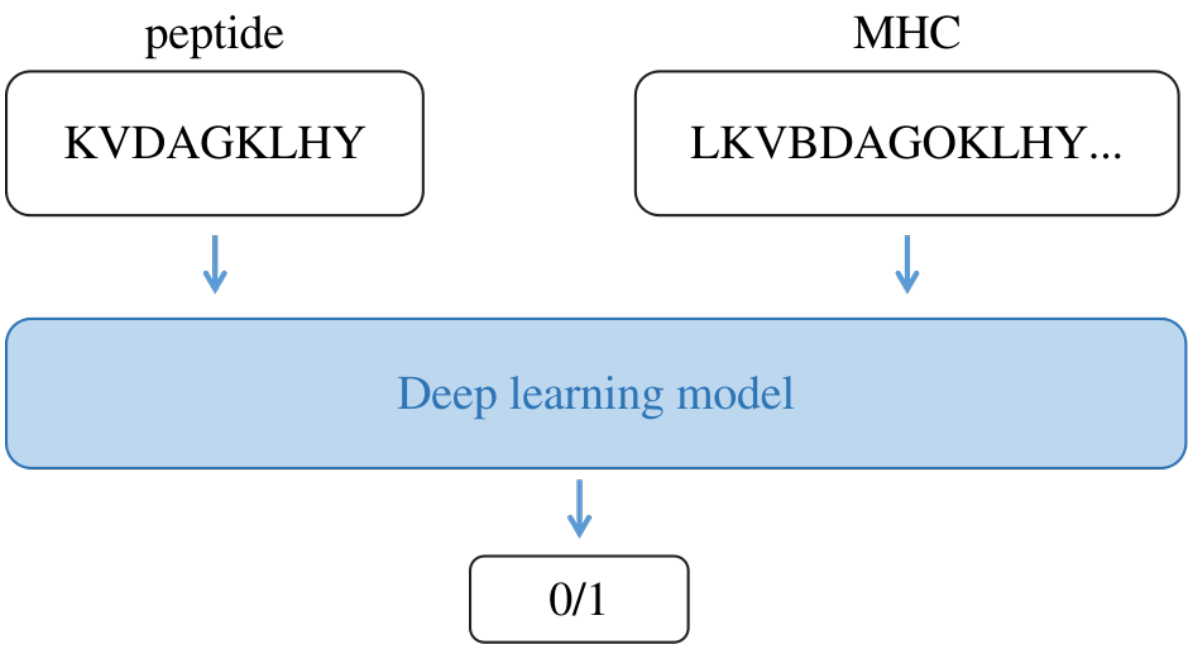
Name	Year ref.	Input	Output
Neopepsee	2018 [44]	RNA-seq, somatic mutations (VCF), HLA type (optional)	Neoantigens and gene expression levels
PGV Pipeline	2018 [45]	DNA-seq	Neoantigens
ScanNeo	2019 [46]	RNA-seq	Neoantigens
NeoPredPipe	2019 [47]	Mutations (VCF) y HLA type	Neoantigens and variant annotation
pVACtools	2020 [48]	Mutations (VCF)	Neoantigens
ProGeo-neo	2020 [49]	RNA-seq y somatic mutations (VCF)	Neoantigens
Neoepiscope	2020 [50]	Somatic mutations (VCF) and BAM files	Neoantigens and mutations
NeoANT-HILL	2020 [51]	RNA-seq y somatic mutations (VCF)	Neoantigens and gene expression levels
NAP-CNB	2021 [52]	RNA-seq	Neoantigens
PEPPRMINT	2021 [53]	DNA-seq	Neoantigens
Valid-NEO	2022 [54]	Somatic mutations (VCF), HLA type (optional)	Neoantigens

Contenido

Discusión

Como se utilizan las técnicas de *deep learning* para la detección de neo antígenos?

La detección de neo antígenos es visto como un problema de clasificación binaría.



Discusión

Que tipos de datos y pre procesamiento es utilizado en la detección de ne antígenos?

Se consideran las cadenas de aminoacidos, como pre procesamiento se utiliza *one-hot encoding* y *BLOSUM*.

A	R	N	...	V
1	0	0		0
0	1	0		0
0	0	1		0
0	0	0		0
0	0	0		0
0	0	0		0
.	.	.		.
.	.	.		.
.	.	.		.
0	0	0		1

	C	S	T	P	A	G	N	D	E	Q	H	R	K	M	I	L	V	F	Y	W
C	0																			
S	-1	4																		
T	-1	1	5																	
P	-3	-1	-1	7																
A	0	1	0	-1	4															
G	-3	0	-2	-2	0	6														
N	-3	-1	0	-2	-2	0	6													
D	-3	1	-1	-1	-2	-1	1	6												
E	-4	0	-1	-1	-1	-2	0	2	5											
Q	-3	0	-1	-1	-1	-2	0	0	2	5										
H	-3	0	-2	-2	-2	-2	1	-1	0	0	8									
R	-3	-1	-1	-2	-1	-2	0	-2	0	1	0	5								
K	-3	-1	-1	-1	-1	-2	0	-1	1	1	-1	2	5							
M	-1	0	-1	-2	-1	-3	-2	-3	-2	0	-2	-1	-1	5						
I	-1	-2	-1	-3	-1	-1	-4	-3	-3	-3	-3	-3	-3	1	4					
L	-1	-2	-1	-3	-1	-4	-3	-4	-3	-2	-3	-2	-2	2	2	4				
V	-1	-2	0	-2	0	-3	-3	-3	-2	-2	-3	-3	-2	1	3	1	4			
F	-2	-2	-2	-4	-2	-3	-3	-3	-3	-3	-1	-3	-3	0	0	0	-1	6		
Y	-2	-2	-2	-3	-2	-3	-2	-3	-2	-1	2	-2	-2	-1	-1	-1	-1	3	7	
W	-2	-3	-2	-4	-3	-2	-4	-4	-3	-2	-2	-3	-3	-1-	-3	-2	-3	1	2	11

Discusión

Que bases de datos son utilizadas en la detección de neo antígenos?

Tabla descrita anteriormente.

Discusión
Bases de datos

Name	Year ref.	Description
VDJdb	2018 [35]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [36]	The bigger database, contains information *T-cell epitopes*
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IPD-IMGT/HLA	2022 [43]	With 25000 MHC molecules and 45 alleles.

Discusión

Que método basado en *deep learning* tiene los mejores resultados?

NetMHCpan4.1 es considerado el método con mejor desempeño. Pero, recientemente, **HLAB** [55] utilizado para *pMHC-I binding prediction*, utiliza BiLSTM, proBERT y *transfer learning* de UniRef100 [56] y BFD [57]; este modelo ha superado a NetMHCpan4.1.

Contenido

Trabajos futuros

Recientemente un trabajo [58] tambien propone el uso de *transfer learning* pero de un modelo pre-entrenado con 250 millones de proteínas. Entonces, se plantea utilizar la propuesta de HLAB, aumentar la cantidad de muestras y evaluar los resultados.

Actualmente se cuenta con una base de datos de proteínas MHC [39], entonces utilizando AlphaFold de Google, se plantea predecir la estructura de varios péptidos y analizar el enlace péptido-MHC desde un punto de vista de la computación gráfica.

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Questions?