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 interno en colaboración con la UCSP

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Proyecto
Financiamiento

Proyecto

Duración y equipo de trabajo

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

Variantes y Mutaciones

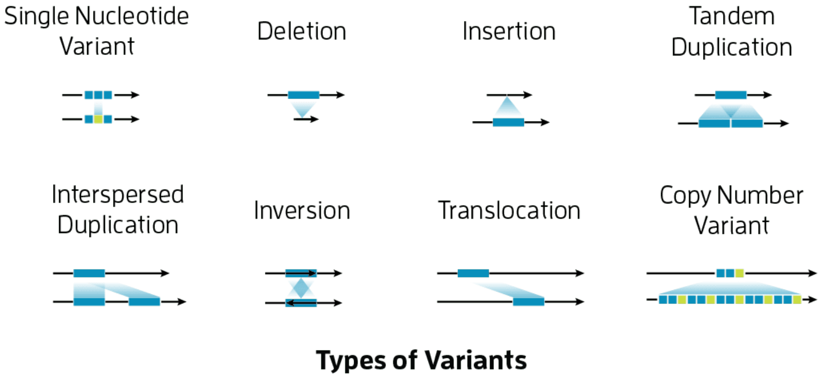


Figure: Example of structural variants. Source: [1]

Inmunoterapia del Cáncer

Es un tipo de tratamiento contra el Cáncer que estimula las defensas naturales del cuerpo para combatir el Cáncer [2].

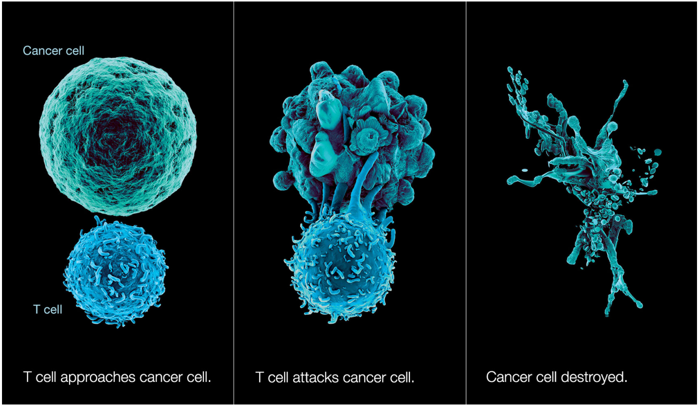


Figure: Ejemplo de como una célula T destruye células del cancer [3].

Inmunoterapia del Cáncer

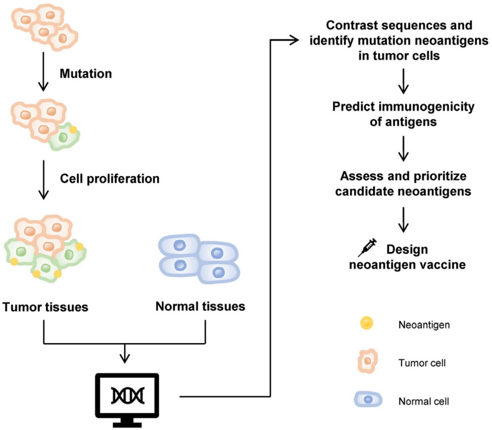
Neo antígenos

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** [4, 5].

En la actualidad hay varios métodos para detectar a predecir neo antígenos, pero **solo una pequeña cantidad de ellos** logran estimular al sistema inmune [6, 7].

Inmunoterapia del Cáncer

Generación de vacunas



Mutation

Cell proliferation

Tumor tissues

Normal tissues

Contrast sequences and identify mutation neoantigens in tumor cells

Predict immunogenicity of antigens

Assess and prioritize candidate neoantigens

Design neoantigen vaccine

● Neoantigen

Tumor cell

Normal cell

Figure: Proceso para la generación de vacunas personalizadas [8].

MHC-I

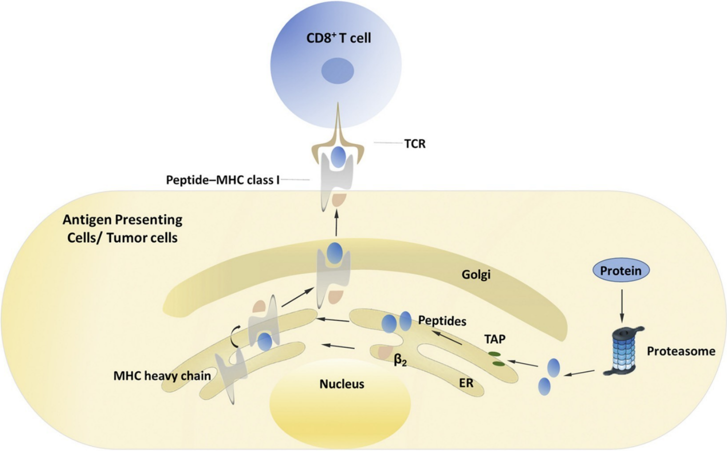


Figure: Presentación de antígenos por MHC-I. Fuente: [9]

Motivación

El cáncer representa el mayor problema de salud mundial, pero lamentablemente los métodos basados en cirugías, radioterapias, quimioterapias tienen baja efectividad [8].

La inmunoterapia del cáncer es una alternativa para el desarrollo de vacunas personalizadas, pero este proceso depende de una correcta detección de neo antígenos [10, 8].

Problema

Menos del 3% de los neoantígenos detectados logran activar a las células T (sistema inmune) [10].

Objetivo general

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

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Preguntas de investigación

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).	

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Metodología

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**

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Convolutional Neural Networks

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

Year	Ref.	Approach	Name	MHC	Encoding
2022	[11]	pMHC(b)	DeepMHCII	II	PFR
2021	[12]	pMHC(b)	DeepImmuno	I	AAindex1
2021	[13]	pMHC(p)	APPM	I	One-hot
2021	[14]	pMHC(p)	MHCfovea	I	One-hot
2021	[15]	pMHC(b)	CNN-PepPred	II	BLOSUM
2020	[16]	pMHC(b)	IConMHC	I	PCA and AAindex3
2020	[17]	pMHC(b)	OnionMHC	I	BLOSUM and structural features
2020	[18]	pMHC(p)	MINERVA	I	Physicochemical properties
2019	[19]	pMHC(b)	CNN-NF	I	Sequence, Hydropathy, Polarity, Length
2019	[20]	pMHC(b)	DeepSeqPan	I	One-hot
2018	[21]	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	[22]	pMHC(b)	DeepNetBim	I	BLOSUM
2021	[23]	pMHC(b)	Deep Attention Pan	I	BLOSUM
2019	[24]	pMHC(b)	ACME	I	BLOSUM
2020	[25]	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	[26]	pMHC(b)	MATHLA	I	BLOSUM
2021	[27]	pMHC(b)	DeepSeqPanII	II	One-hot and BLOSUM
2021	[28]	pMHC(b)	GRU-based RNN	II	Embeding layer
2021	[29]	pMHC(b)	BVLSTM-MHC	I	One-hot and BLOSUM
2020	[30]	pMHC(b)	MHCnuggets	I, II	One-hot
2019	[31]	pMHC(b)	DeepHLApan	I	One-hot

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Transformers

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

Year	Ref.	Approach	Name	MHC	Encoding
2022	[32]	pMHC(b)	MHCRoBERTa	I	Tokenized from a pre-trained model
2022	[33]	pMHC(b)	TransPHLA	I	Character embedding model
2021	[34]	pMHC(b)	BERTMHC	II	Embeding layer
2021	[35]	pMHC(p)	ImmunoBERT	I	Embeding layer

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Bases de datos

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

Name	Year ref.	Description
VDJdb	2018 [36]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [37]	The bigger database, contains information *T-cell epitopes*
TSNAdb	2018 [38]	It contains 7748 samples of mutations and HLA of 16 types of cancer.
NeoPeptide	2019 [39]	It contains samples of neoantigens resulting from somatic mutations and related items. 1818137 epitopes of more than 36000 neoantigens.
pHLA3D	2019 [40]	Presents 106 3D structures of the alpha, *beta*2*M* chains, and peptides of HLA-I molecules
dbPepNeo	2020 [41]	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 [42]	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 [43]	Tool for building databases on *peptide-MHC binding*. It uses data from *Mass Spectrometry*.
IPD-IMGT/HLA	2022 [44]	With 25000 MHC molecules and 45 alleles.

Revisión Sistemática

Pipelines

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

Name	**Year ref.**	**Input**	**Output**
Neopepsee	2018 [45]	RNA-seq, somatic mutations (VCF), HLA type (optional)	Neoantigens and gene expression levels
PGV Pipeline	2018 [46]	DNA-seq	Neoantigens
ScanNeo	2019 [47]	RNA-seq	Neoantigens
NeoPredPipe	2019 [48]	Mutations (VCF) y HLA type	Neoantigens and variant annotation
pVACtools	2020 [49]	Mutations (VCF)	Neoantigens
ProGeo-neo	2020 [50]	RNA-seq y somatic mutations (VCF)	Neoantigens
Neoepiscope	2020 [51]	Somatic mutations (VCF) and BAM files	Neoantigens and mutations
NeoANT-HILL	2020 [52]	RNA-seq y somatic mutations (VCF)	Neoantigens and gene expression levels
NAP-CNB	2021 [53]	RNA-seq	Neoantigens
PEPPRMINT	2021 [54]	DNA-seq	Neoantigens
Valid-NEO	2022 [55]	Somatic mutations (VCF), HLA type (optional)	Neoantigens

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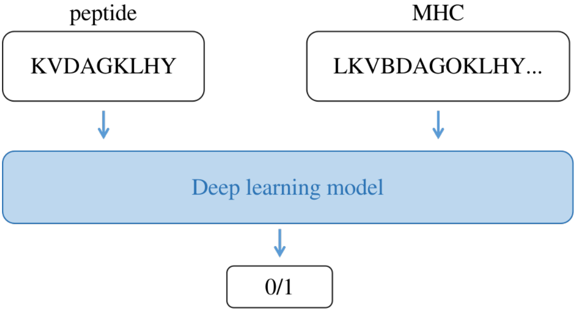
Discusión

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

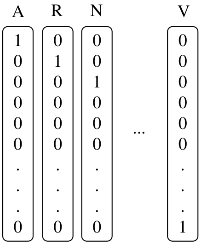
La detección de neo antígenos es visto como un problema de clasificación binaría.



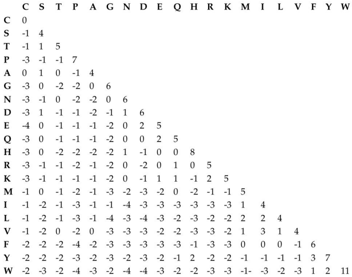
Discusión

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*.



$$\begin{array}{ccccc} A & R & N & & V \\ 1 & 0 & 0 & & 0 \\ 0 & 1 & 0 & & 0 \\ 0 & 0 & 1 & & 0 \\ 0 & 0 & 0 & & 0 \\ 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & & 1 \end{array}$$



	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 [36]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [37]	The bigger database, contains information *T-cell epitopes*
TSNAdb	2018 [38]	It contains 7748 samples of mutations and HLA of 16 types of cancer.
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IPD-IMGT/HLA	2022 [44]	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** [56] utilizado para *pMHC-I binding prediction*, utiliza BiLSTM, proBERT y *transfer learning* de UniRef100 [57] y BFD [58]; este modelo ha superado a NetMHCpan4.1.

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Recientemente un trabajo [59] 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 [40], 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?