Universidad Nacional de San Agustín

Detección *in Silico* de Neoantígenos Utilizando Transformers y Transfer Learning en el Marco de Desarrollo de Vacunas Personalizadas para Tratar el Cáncer

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Contexto y Motivación

An la actualidad, el cáncer representa el mayor problema de salud mundial [1].

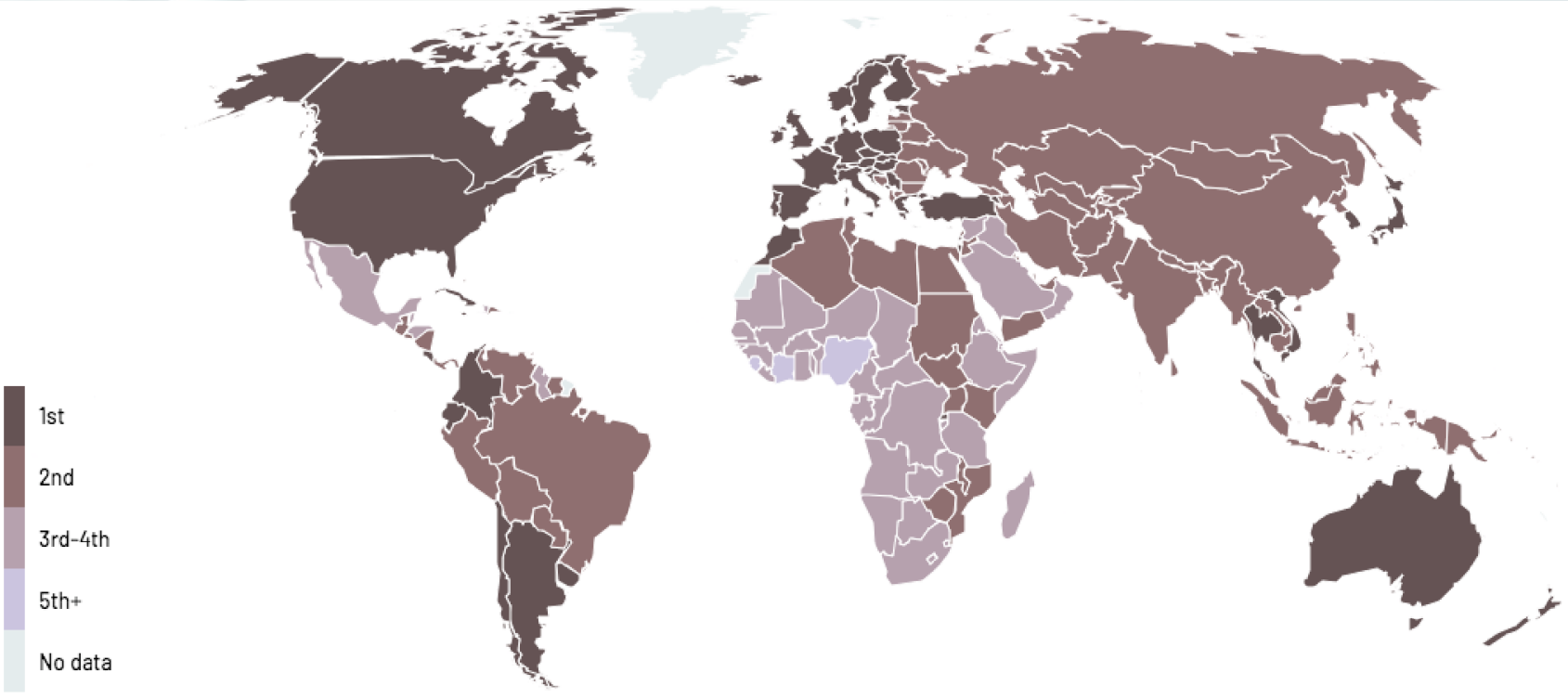

Figure: Ranking de las muertes por cáncer entre 30 y 69 años. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación

Muertes por tipos de cáncer

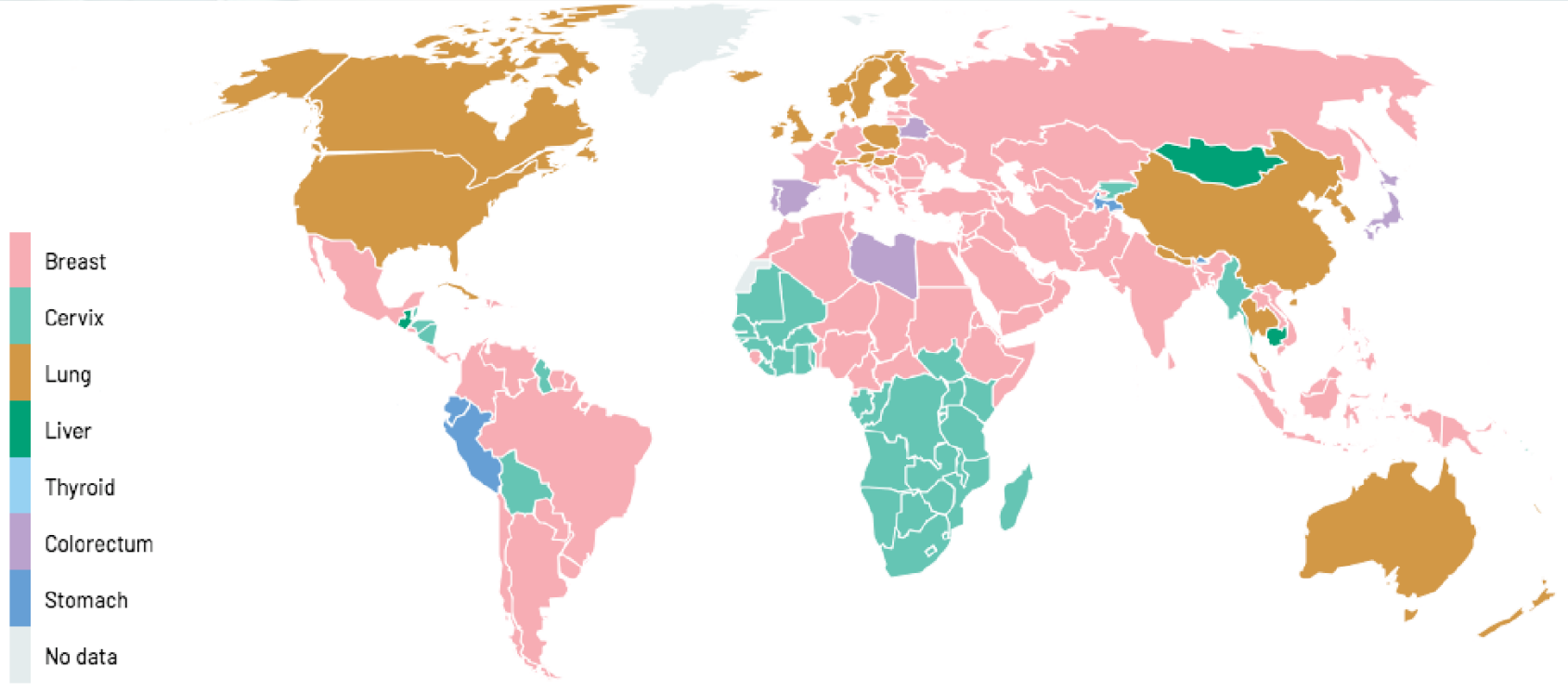

Figure: Ranking de las muertes por tipo de cáncer en mujeres. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación

Muertes por tipos de cáncer

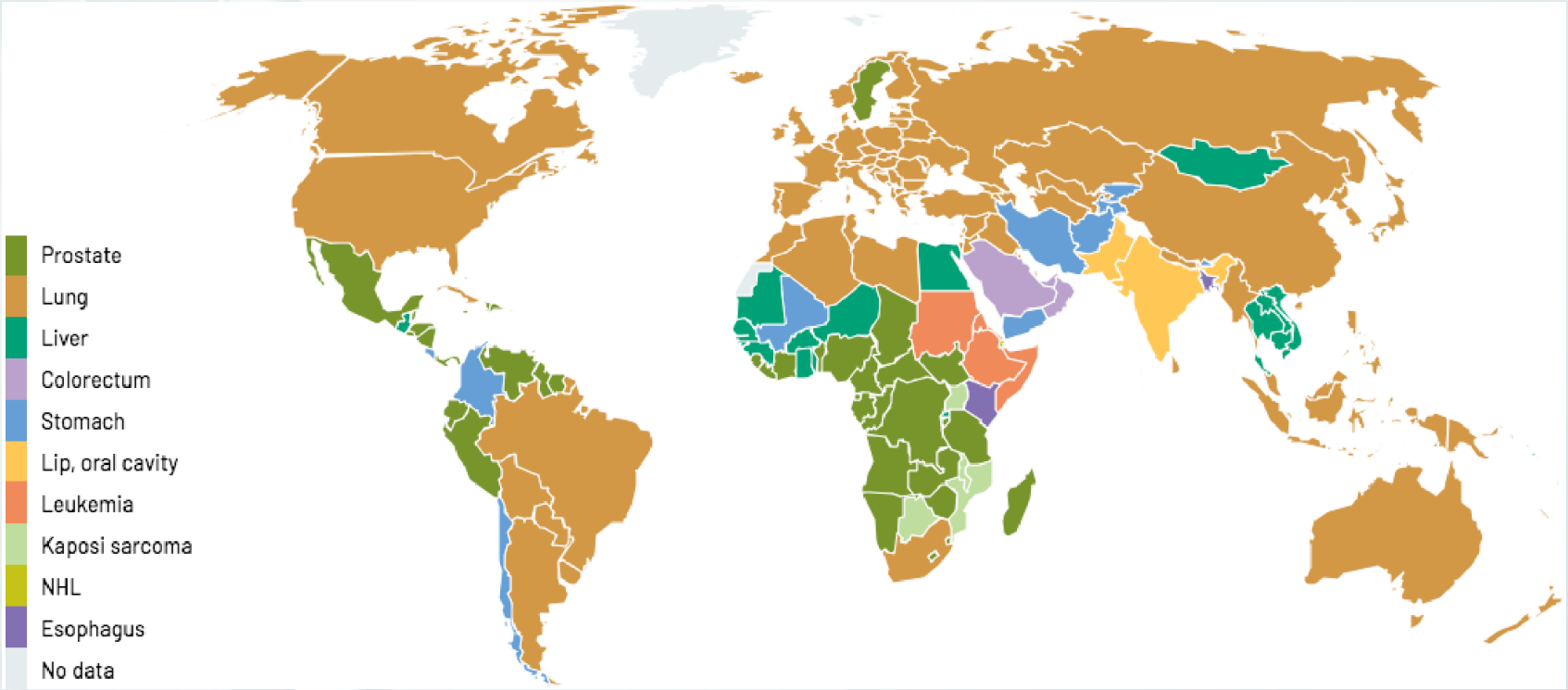

Figure: Ranking de las muertes por tipo de cáncer en hombres. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación
Porcentaje de casos y muertes

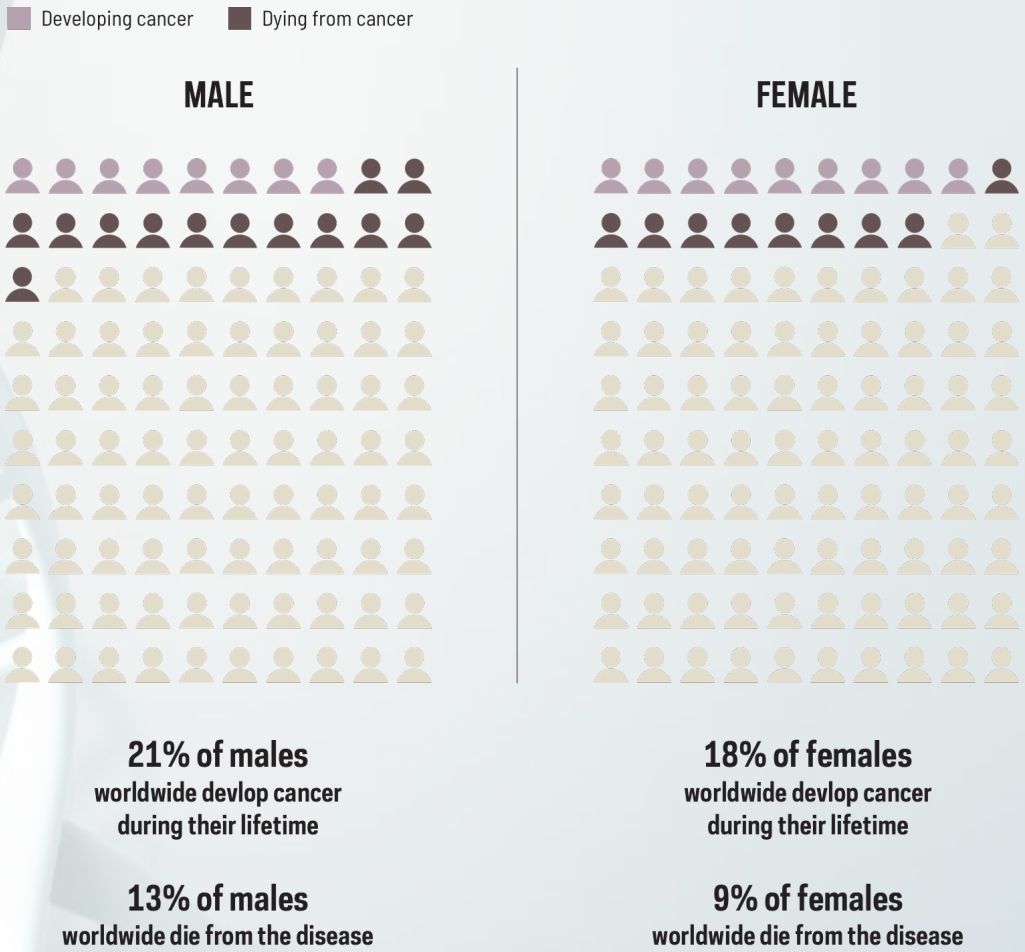

Figure: Porcentaje de casos y muertes por sexo. **Fuente** The Atlas Cancer [2].

Contexto y Motivación

Predicción de nuevos casos

Figure: Predicción de nuevos casos para el 2040. **Fuente** The Atlas Cancer [2].

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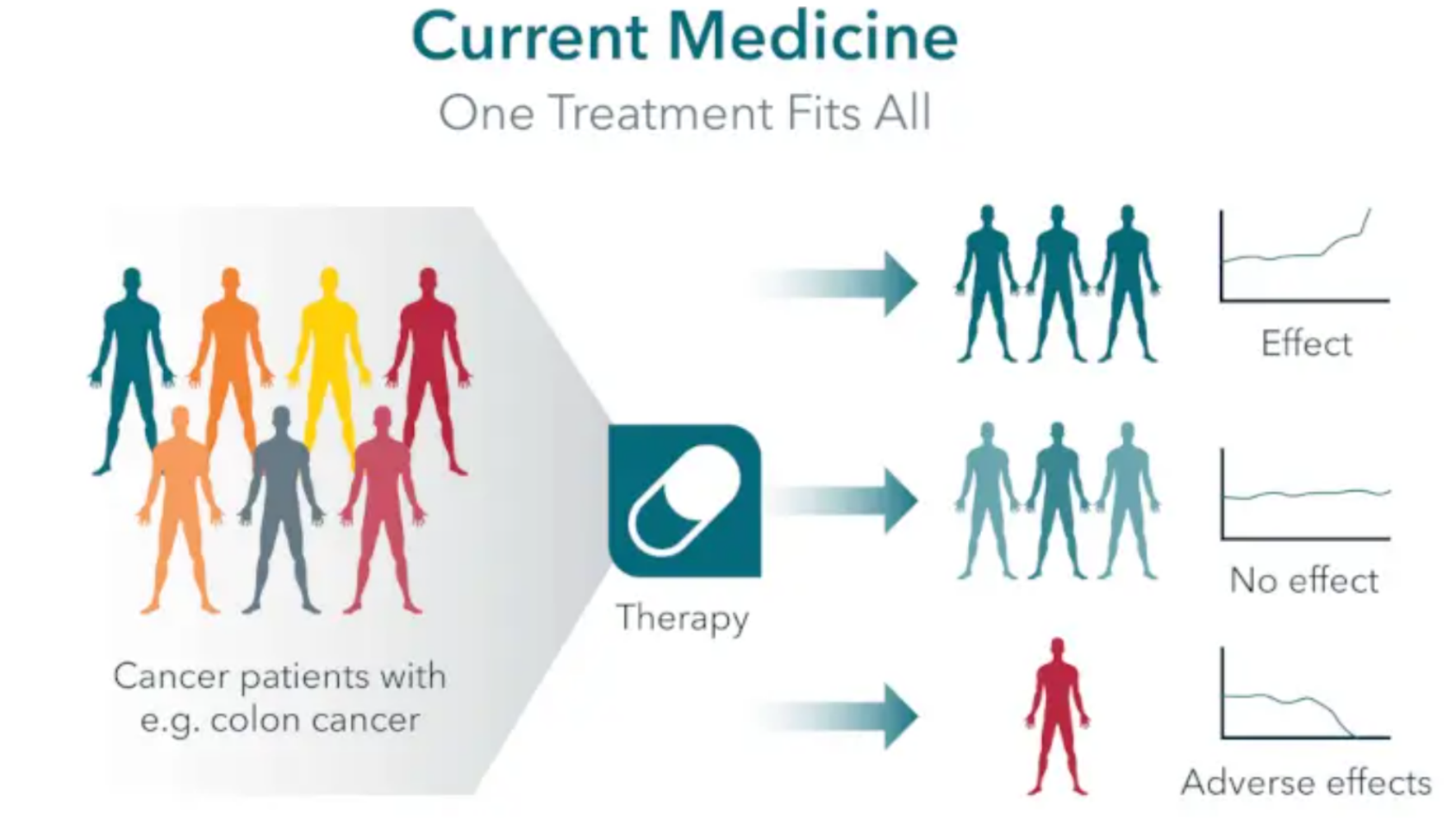

Figure: Pacientes con el mismo tipo de cáncer pueden reaccionar de forma disitinta a los mismos tratamientos. **Fuente** The Atlas Cancer [3].

Contexto y Motivación

Reacciones distintas para cada paciente

Figure: Cada paciente necesita un tratamiento personalizado. **Fuente** The Atlas Cancer [3].

Inmunoterapia del Cáncer

Es un tipo de tratamiento contra el Cáncer que estimula las defensas naturales del cuerpo para combatir el Cáncer [4].

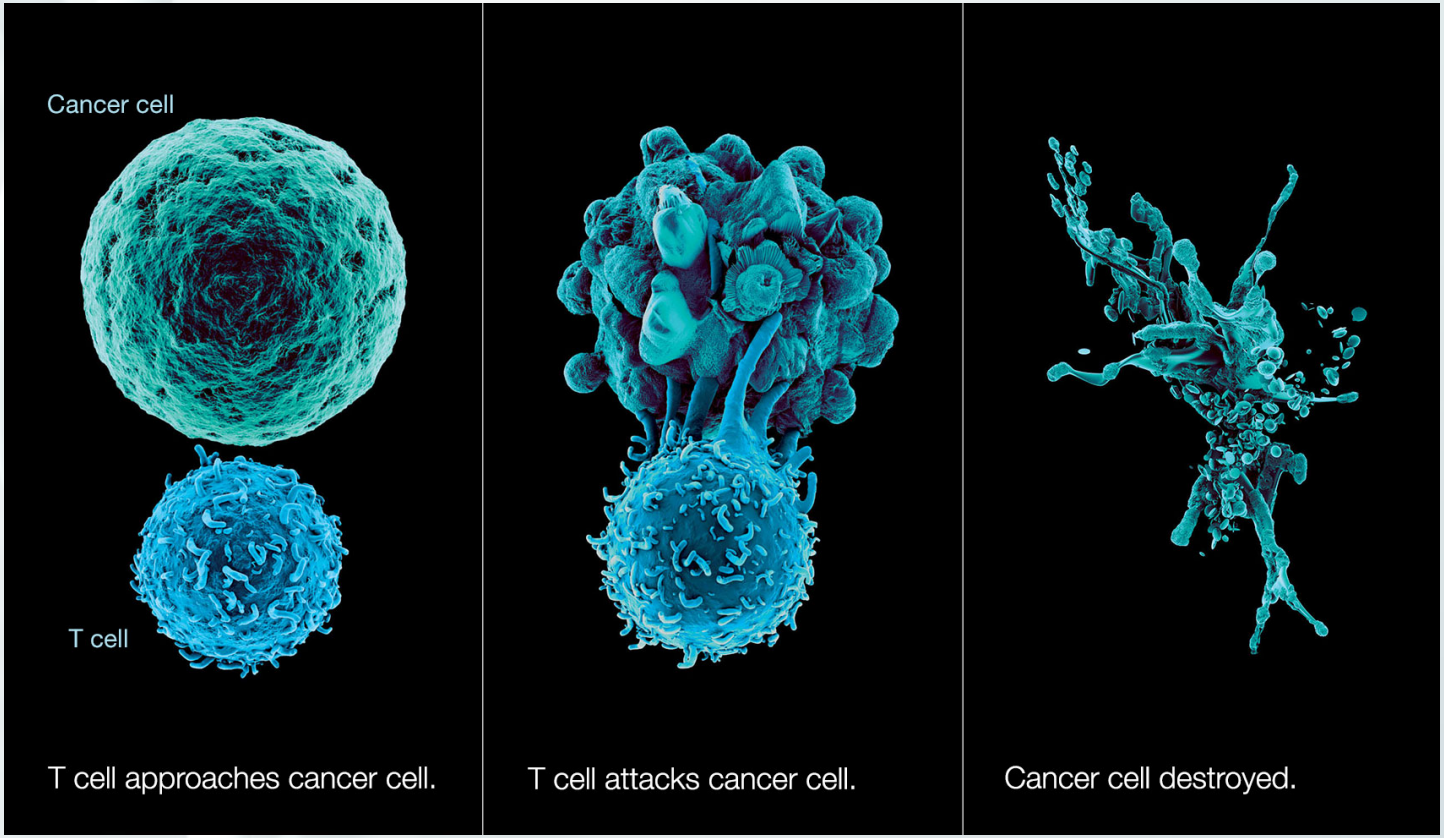

Figure: Ejemplo de como una célula T destruye células del cancer [5].

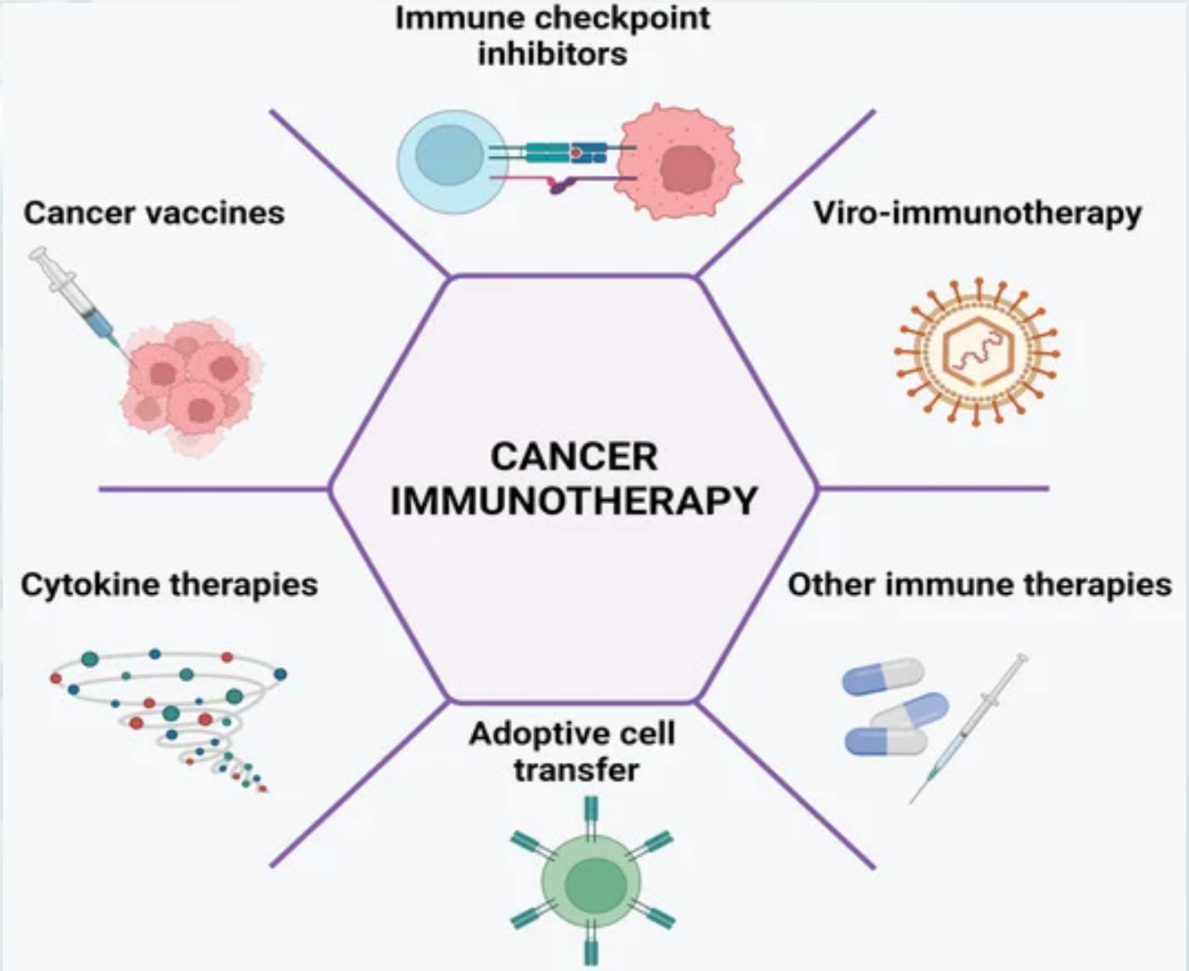

Figure: Tipos de tratamientos para la inmunoterapia del cáncer. **Fuente**: [6].

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Es una **proteína** que se forma en las células de Cáncer cuando ocurre mutaciones en el DNA [7, 8].

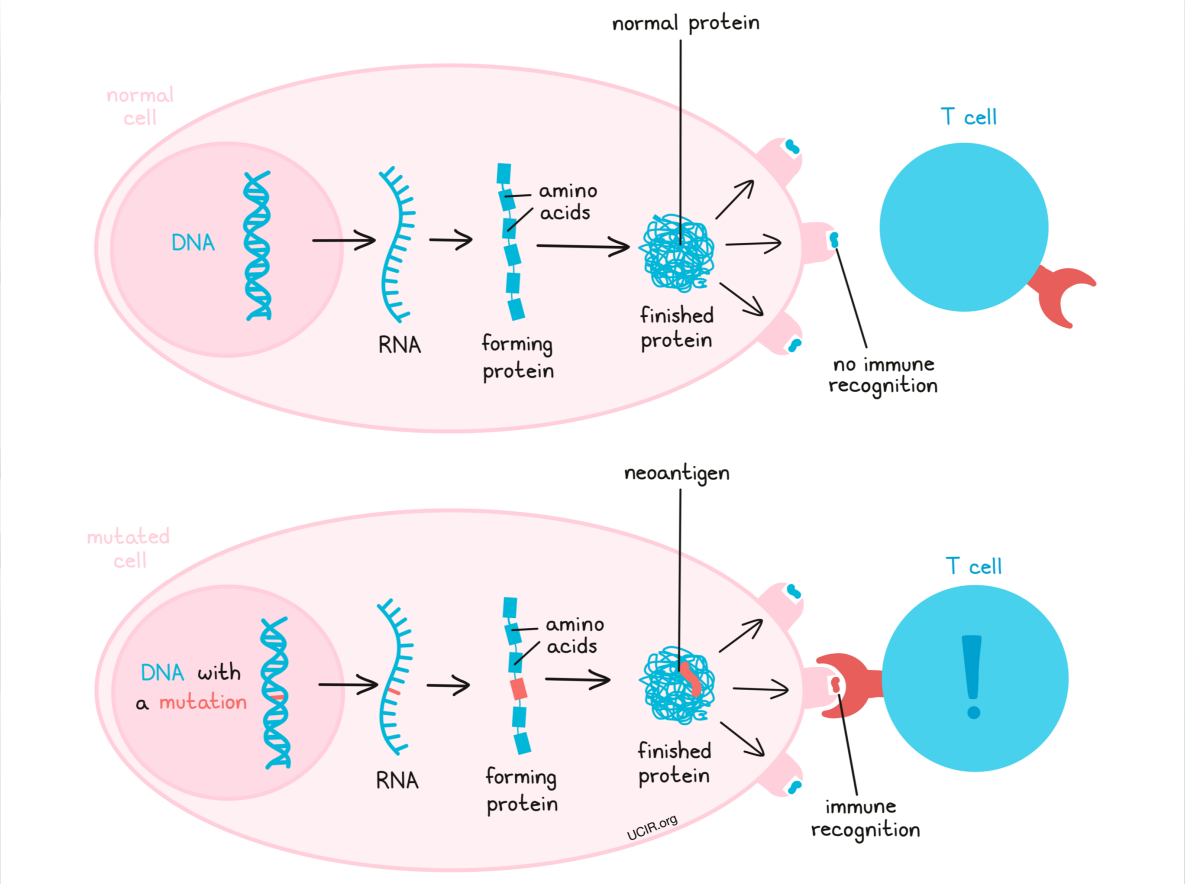

Figure: Neoantígenos y células T. **Fuente**: [9].

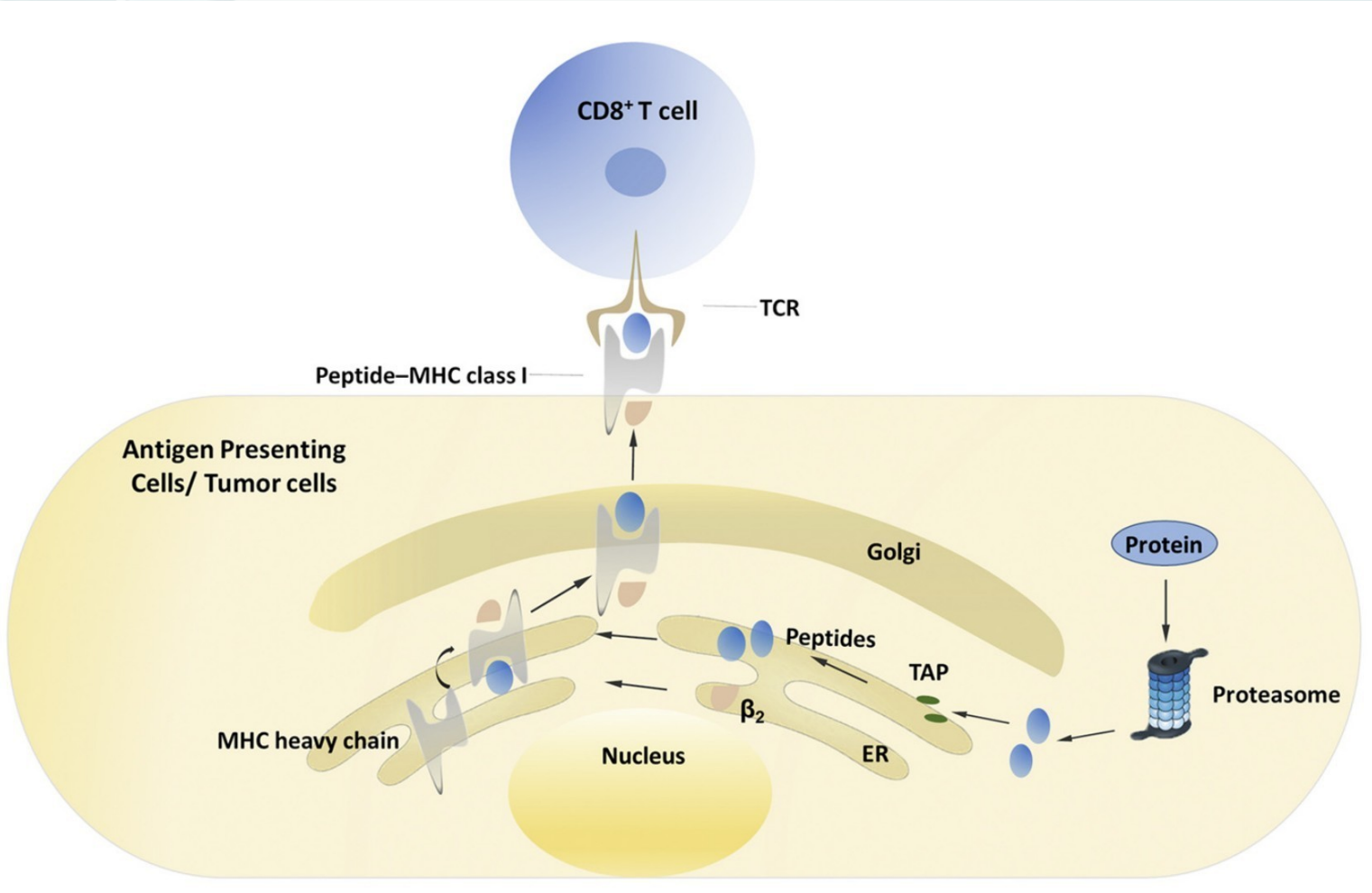

Figure: Presentación de antígenos por MHC-I. Fuente: [10]

Contexto y Motivación
Vacunas personalizadas

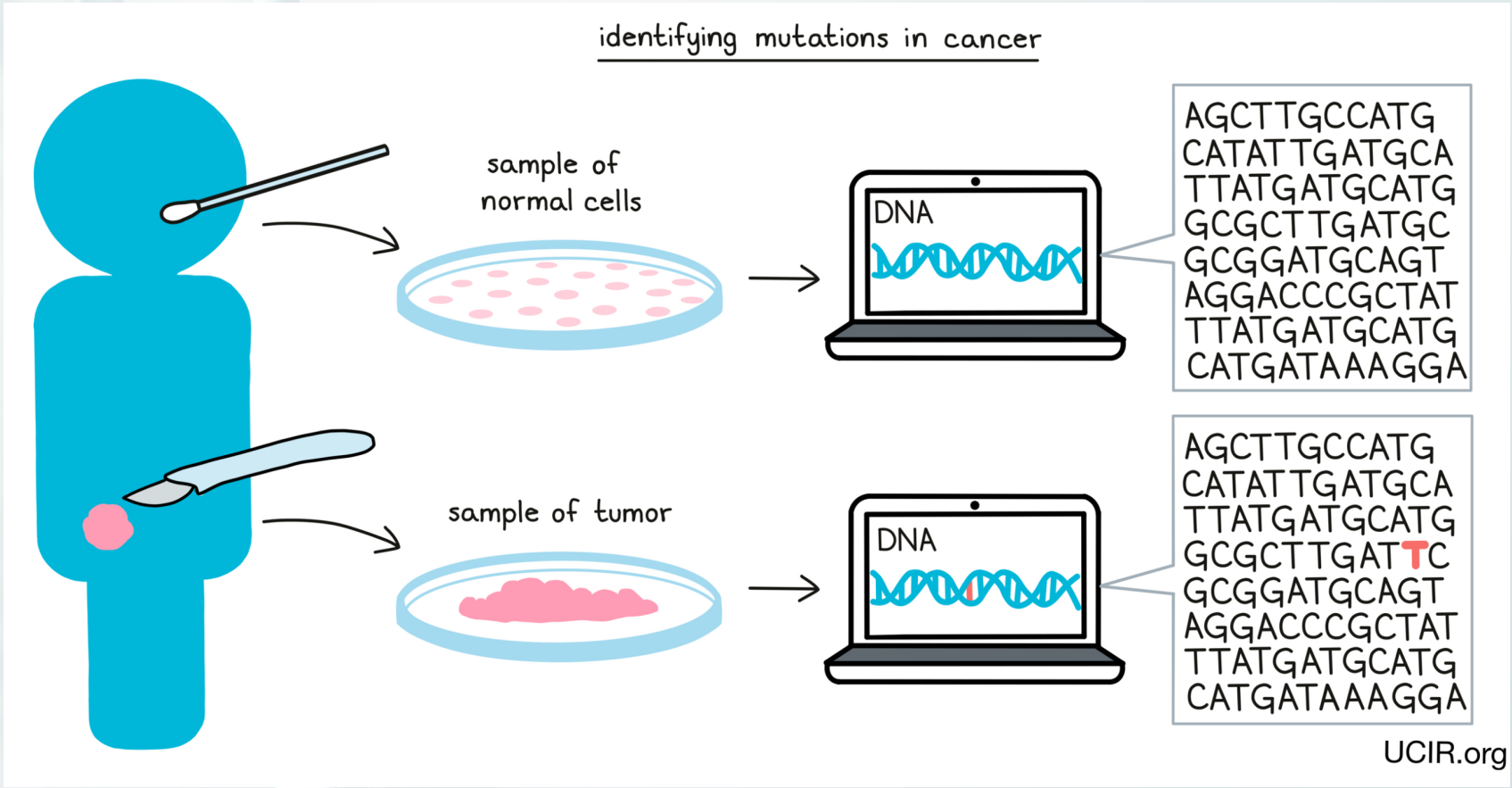

Figure: Proceso para la generación de vacunas contra el cáncer. **Fuente**: [9].

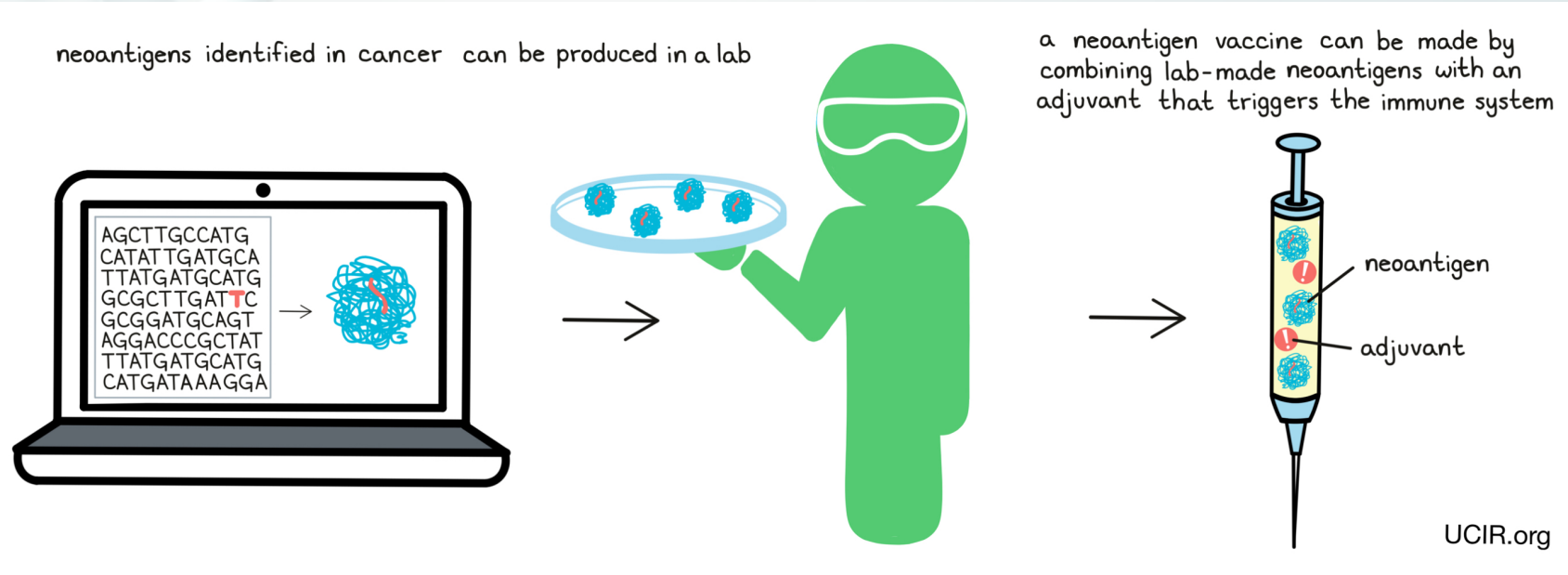

Figure: Proceso para la generación de vacunas contra el cáncer. **Fuente**: [9].

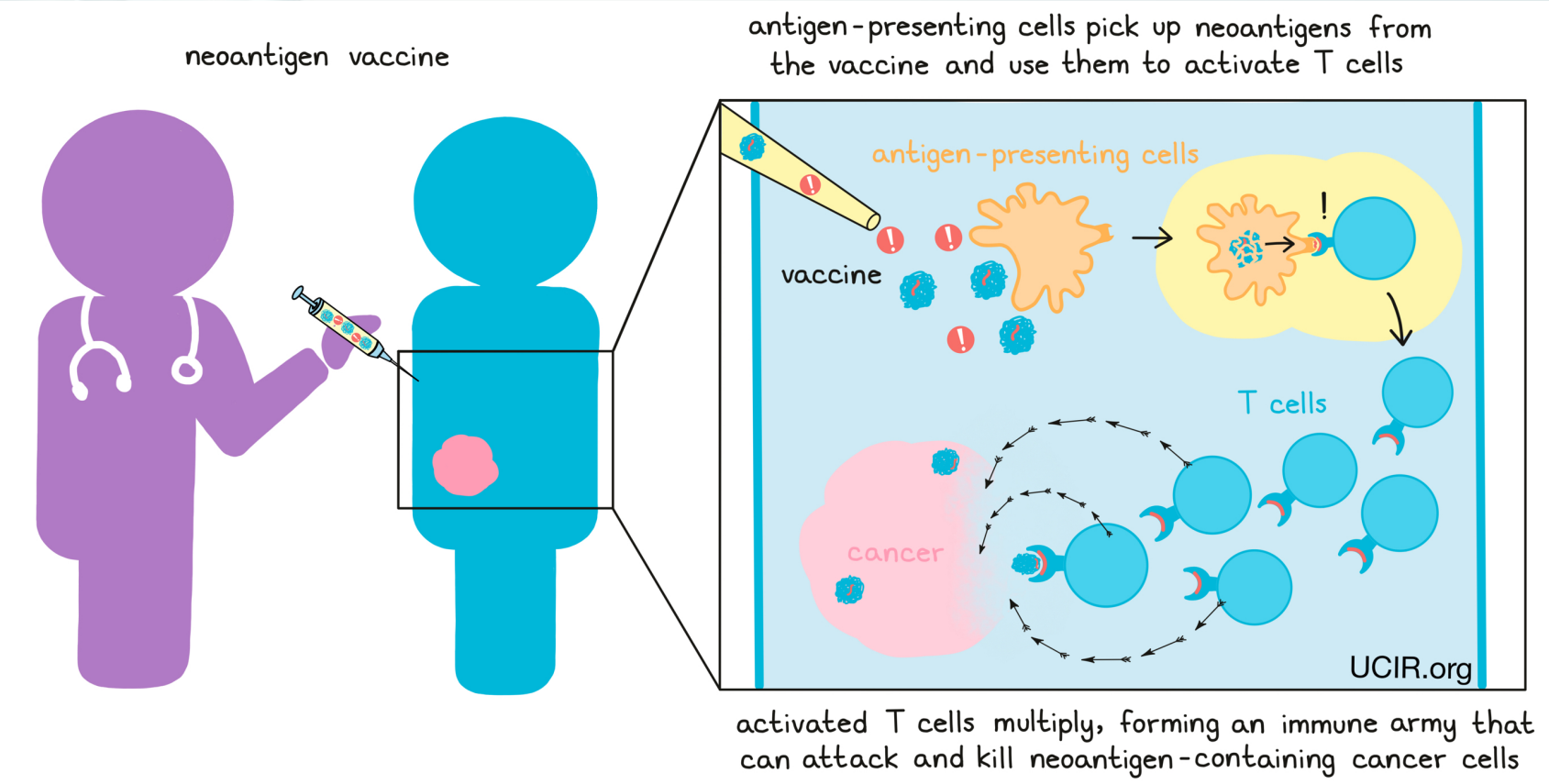

Figure: Proceso para la generación de vacunas contra el cáncer. **Fuente**: [9].

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Vacunas personalizadas

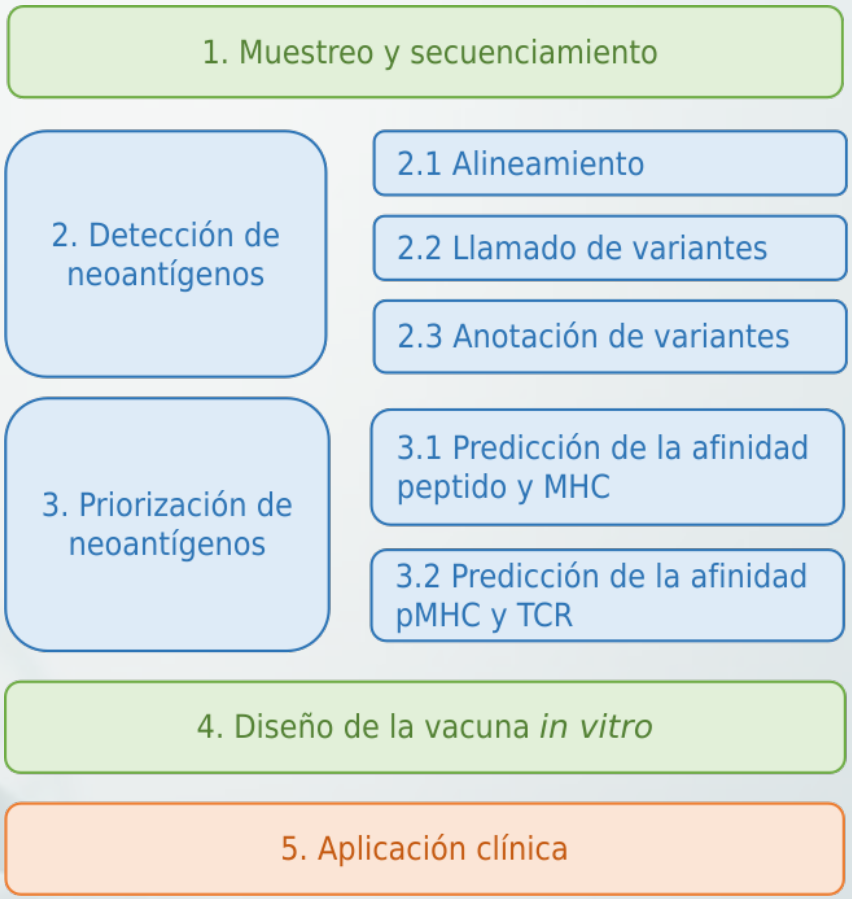

Figure: Resumen del proceso de generación de vacunas contra el cáncer.

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Motivación

El cáncer representa el mayor problema de salud mundial, pero lamentablemente los métodos basados en cirugías, radioterapias, quimioterapias tienen baja efectividad [11].

La inmunoterapia del cáncer es una alternativa para el desarrollo de vacunas personalizadas, pero este proceso depende de una correcta detección de neo antígenos [12, 11].

Problema

Menos del **5% de péptidos** detectados en *pMHC binding*, llegan a la membrana de la células. Para *peptide-MHC presentation*, propuestas recientes solo llegan a **0.6 de *presicion* y 0.4 de *recall*** [13].

En este contexto, la tesis se enfoca en el problema de *pMHC presentation*, considerándolo como un problema de clasificación binaria, y tomando como entrada la secuencia de aminoácidos del péptido y la secuencia de aminoácidos de la proteína MHC.

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Objetivo general

Proponer un método basado en *deep learning* para la detección de neo antígenos, enfocados en el problema de *peptide-MHC presentation*.

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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. Sobre *deep learning* La metodología es detallada. Tiene repositorio de código fuente y base de datos (deseable).	Trabajos de baja calidad, que no esten rankeados.

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

Year	Ref.	Approach	Name	MHC	Encoding
2022	[14]	pMHC(b)	DeepMHCII	II	PFR
2021	[15]	pMHC(b)	DeepImmuno	I	AAindex1
2021	[16]	pMHC(p)	APPM	I	One-hot
2021	[17]	pMHC(p)	MHCfovea	I	One-hot
2021	[18]	pMHC(b)	CNN-PepPred	II	BLOSUM
2020	[19]	pMHC(b)	IConMHC	I	PCA and AAindex3
2020	[20]	pMHC(b)	OnionMHC	I	BLOSUM and structural features
2020	[21]	pMHC(p)	MINERVA	I	Physicochemical properties
2019	[22]	pMHC(b)	CNN-NF	I	Sequence, Hydropathy, Polarity, Length
2019	[23]	pMHC(b)	DeepSeqPan	I	One-hot
2018	[24]	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	[25]	pMHC(b)	DeepNetBim	I	BLOSUM
2021	[26]	pMHC(b)	Deep Attention Pan	I	BLOSUM
2019	[27]	pMHC(b)	ACME	I	BLOSUM
2020	[28]	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	[29]	pMHC(b)	MATHLA	I	BLOSUM
2021	[30]	pMHC(b)	DeepSeqPanII	II	One-hot and BLOSUM
2021	[31]	pMHC(b)	GRU-based RNN	II	Embeding layer
2021	[32]	pMHC(b)	BVLSTM-MHC	I	One-hot and BLOSUM
2020	[33]	pMHC(b)	MHCnuggets	I, II	One-hot
2019	[34]	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	[35]	pMHC(b)	MHCRoBERTa	I	Tokenized from a pre-trained model
2022	[36]	pMHC(b)	TransPHLA	I	Character embedding model
2021	[37]	pMHC(b)	BERTMHC	II	Embeding layer
2021	[38]	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 [39]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [40]	The bigger database, contains information *T-cell epitopes*
TSNAdb	2018 [41]	It contains 7748 samples of mutations and HLA of 16 types of cancer.
NeoPeptide	2019 [42]	It contains samples of neoantigens resulting from somatic mutations and related items. 1818137 epitopes of more than 36000 neoantigens.
pHLA3D	2019 [43]	Presents 106 3D structures of the alpha, *beta2M* chains, and peptides of HLA-I molecules
dbPepNeo	2020 [44]	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 [45]	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 [46]	Tool for building databases on *peptide-MHC binding*. It uses data from *Mass Spectrometry*.
IPD-IMGT/HLA	2022 [47]	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 [48]	RNA-seq, somatic mutations (VCF), HLA type (optional)	Neoantigens and gene expression levels
PGV Pipeline	2018 [49]	DNA-seq	Neoantigens
ScanNeo	2019 [50]	RNA-seq	Neoantigens
NeoPredPipe	2019 [51]	Mutations (VCF) y HLA type	Neoantigens and variant annotation
pVACtools	2020 [52]	Mutations (VCF)	Neoantigens
ProGeo-neo	2020 [53]	RNA-seq y somatic mutations (VCF)	Neoantigens
Neoepiscope	2020 [54]	Somatic mutations (VCF) and BAM files	Neoantigens and mutations
NeoANT-HILL	2020 [55]	RNA-seq y somatic mutations (VCF)	Neoantigens and gene expression levels
NAP-CNB	2021 [56]	RNA-seq	Neoantigens
PEPPRMINT	2021 [57]	DNA-seq	Neoantigens
Valid-NEO	2022 [58]	Somatic mutations (VCF), HLA type (optional)	Neoantigens

Propuesta

La propuesta se basa el los modelos BERTMHC [37] y APPM [59]. Tambien, se utilizará *transfer learning* de ESM-1b [60], esta red neuronal fue entrenada con 250 millones de proteínas a diferencia de TAPE (utilizada por BERTMHC), que fue entrenada con 30 milllones de proteínas.

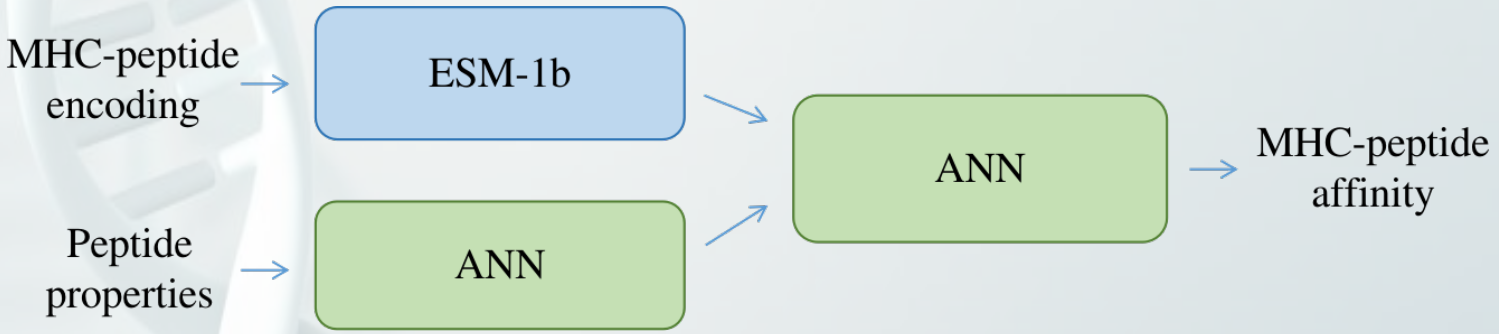


Figure: Proceso general utilizado para la detección de neo antígenos a partir de secuencias de DNA. Fuente: [61].

Propuesta
BERTMHC

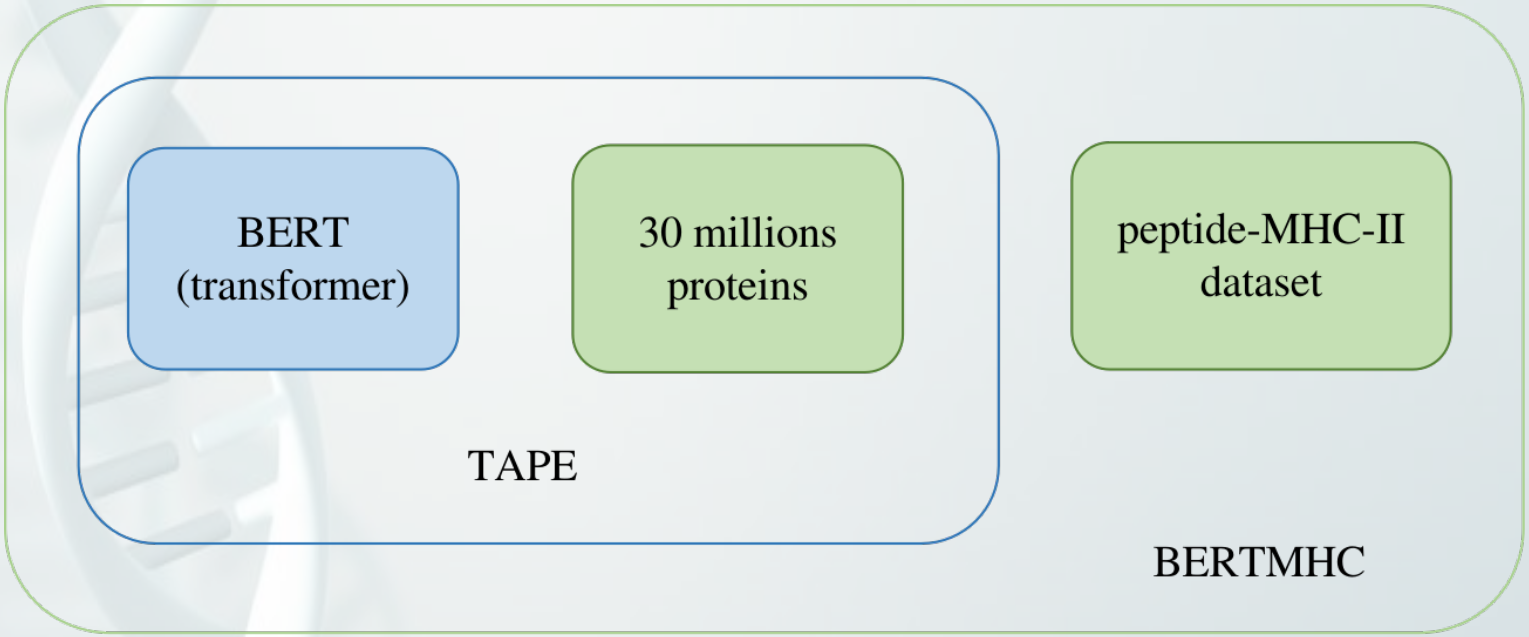


Figure: BERTMHC.

Propuesta
APPM

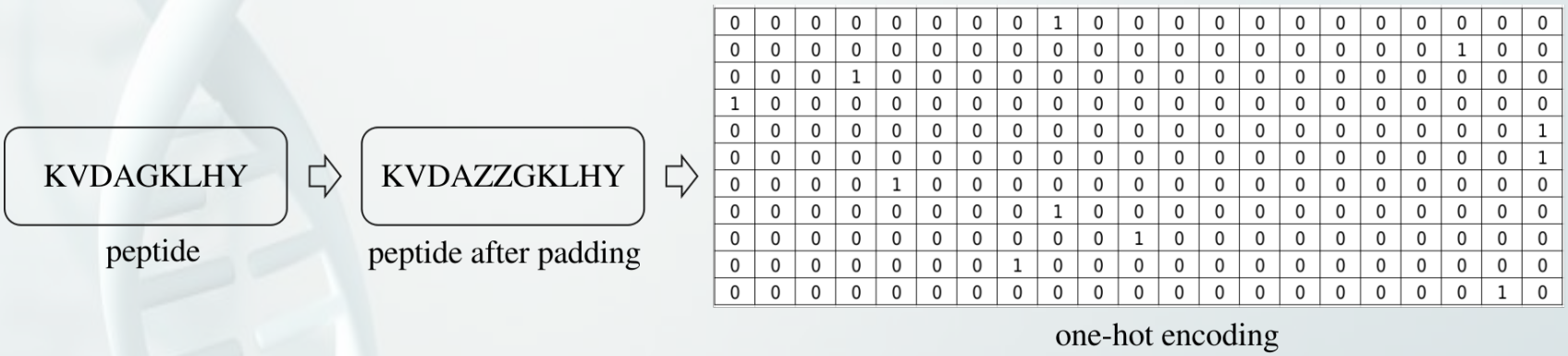


Figure: Proceso para obtener una matriz (imagen) a partir de un péptido (APPM).

MHC alleles utilizados

Table: Cantidad de muestras por tipo de *allele*.

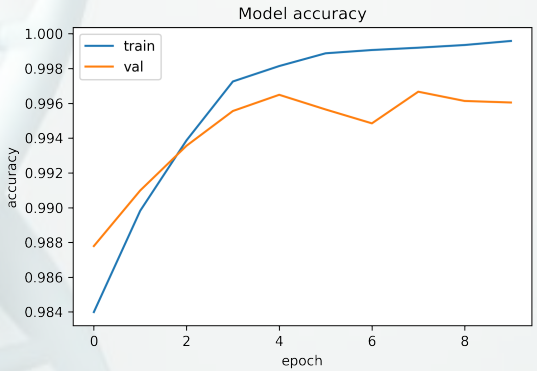
Alleles	**Label = 1**	**Label = 0**	**Train**	**Test**
A*01:01	3398	48700	45498	6600
A*02:01	6779	165342	160921	11200
A*02:03	1780	116299	107879	10200
A*31:01	1879	45918	41597	6200
B*44:02	1525	44760	40085	6200
B*44:03	1487	39482	34769	6200
MHC-II alleles	1917	496	1533	384

Resultados

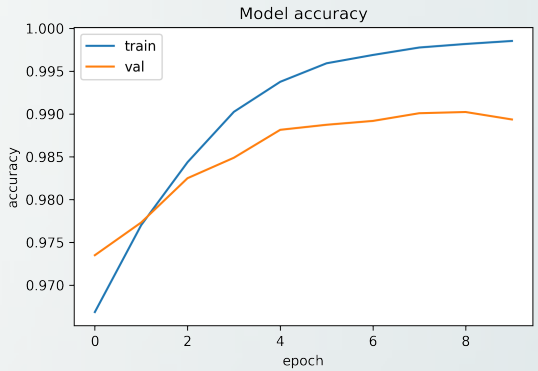
Table: Resultados obtenidos en cada base de datos.

Allele	*Accuracy*	*F1 score*	*Precision*	*Recall*
A*01:01	0.978	0.917	0.982	0.887
A*0201	0.962	0.956	0.965	0.948
A*02:03	0.992	0.979	0.994	0.969
A*31:01	0.980	0.968	0.989	0.951
B*44:02	0.991	0.981	0.968	0.997
B*44:03	0.992	0.987	0.995	0.980

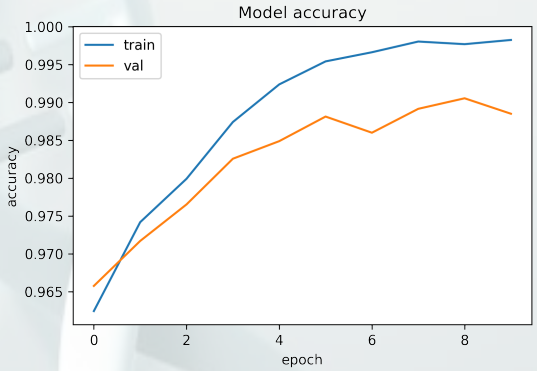
Resultados



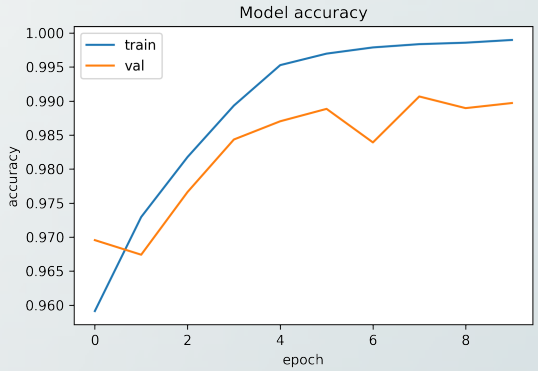
(a) A*01:01



(b) A*02:01



(c) A*02:03



(d) A*31:01

Figure: *Accuracy* durante cada *epoch*, para cada base de datos. Las bases de datos representan las células HLA A*01:01, A*02:01, A*02:03, A*31:01.

Conclusiones

Se ha desarrollado una RSL, sobre los métodos de detección de neoantígenos utilizando *deep learning*. Esto ha logrado identificar las tendencias, retos y problemas del tema de interes.

Se ha realizado experimentos preliminares, sobre el uso de CNNs para el problema de peptide-MHC presentation. Se ha utilizado muestras de MS con un enfoque *single allele* (se entrena varios modelos para cada tipo de MHC).

Trabajos futuros

Recientemente un trabajo [62] tambien propone el uso de *transfer learning* pero de un modelo pre-entrenado con 250 millones de proteínas. Entonces, se plantea utilizar la misma red, aumentar la cantidad de muestras y evaluar los resultados.

Actualmente se cuenta con una base de datos de proteínas MHC [43], 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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