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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2023

Contenido

Contenido

Contexto y Motivación

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

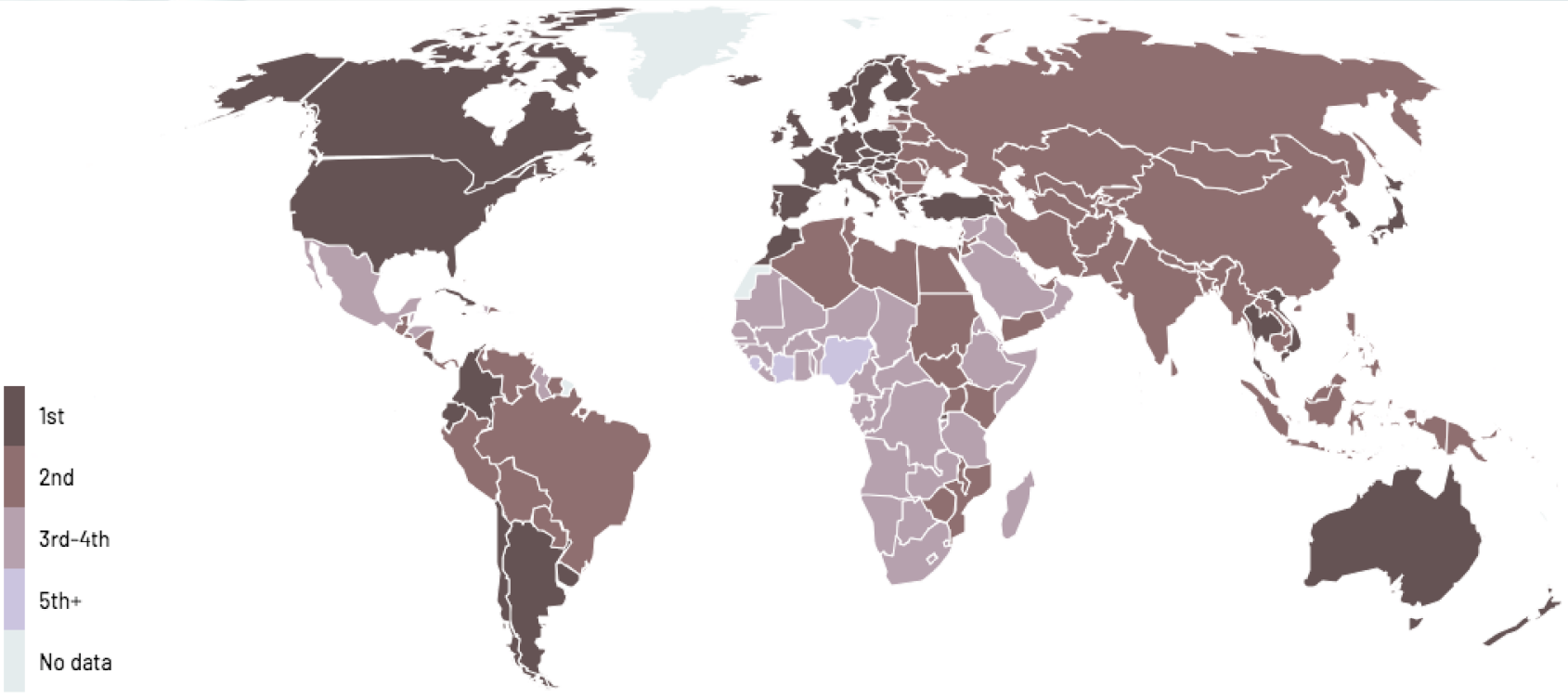


Figure: Ranking de las muertes por cáncer entre 30 y 69 años. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación
Muertes por tipos de cáncer

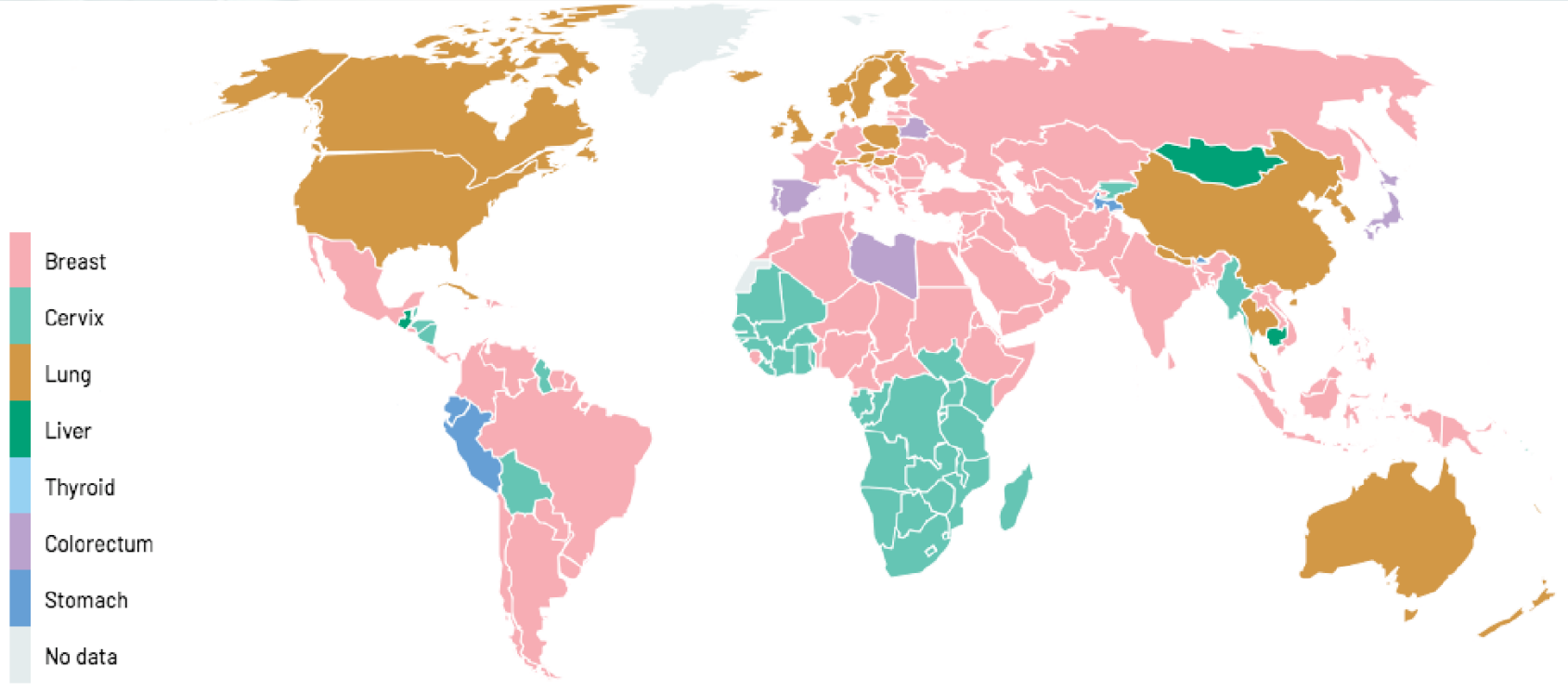


Figure: Ranking de las muertes por tipo de cáncer en mujeres. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación

Muertes por tipos de cáncer

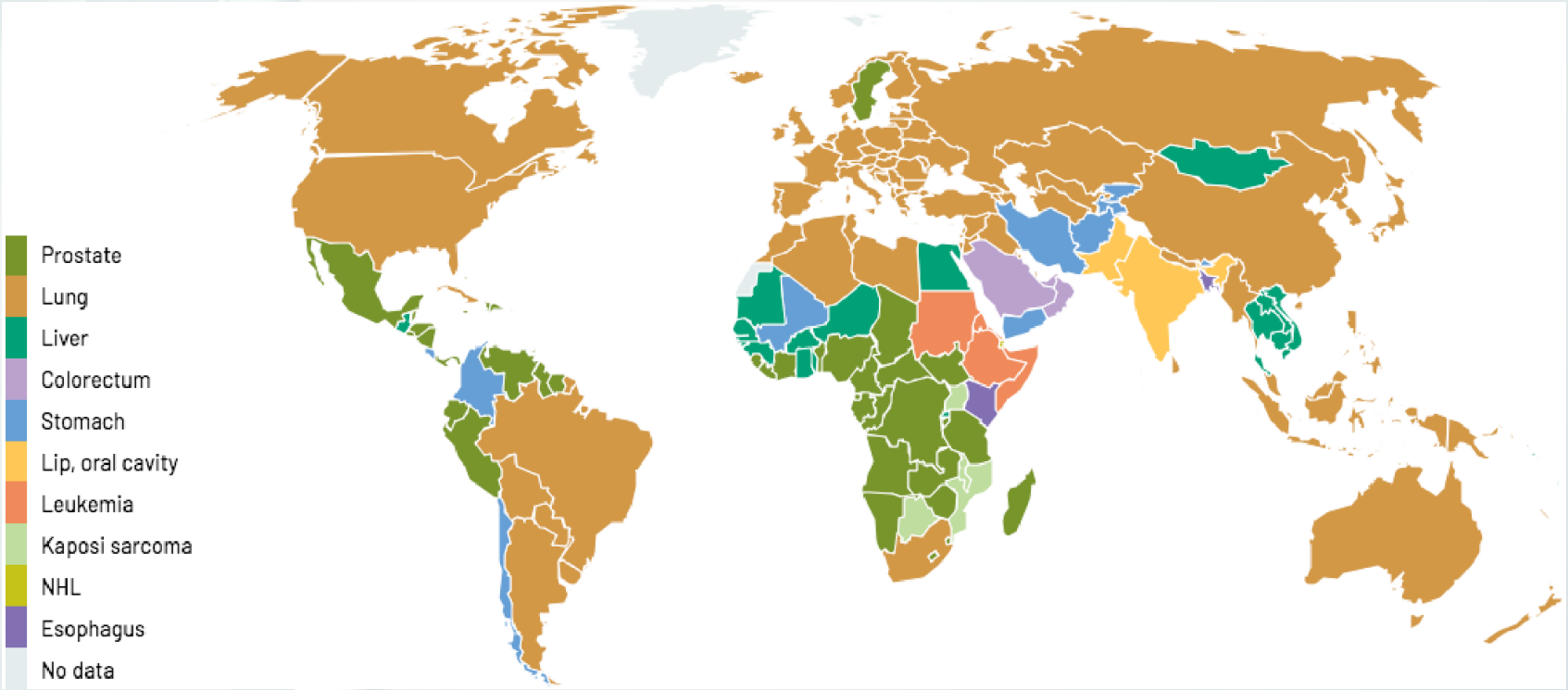


Figure: Ranking de las muertes por tipo de cáncer en hombres. **Fuente**: The Atlas Cancer [2].

Contexto y Motivación

Porcentaje de casos y muertes

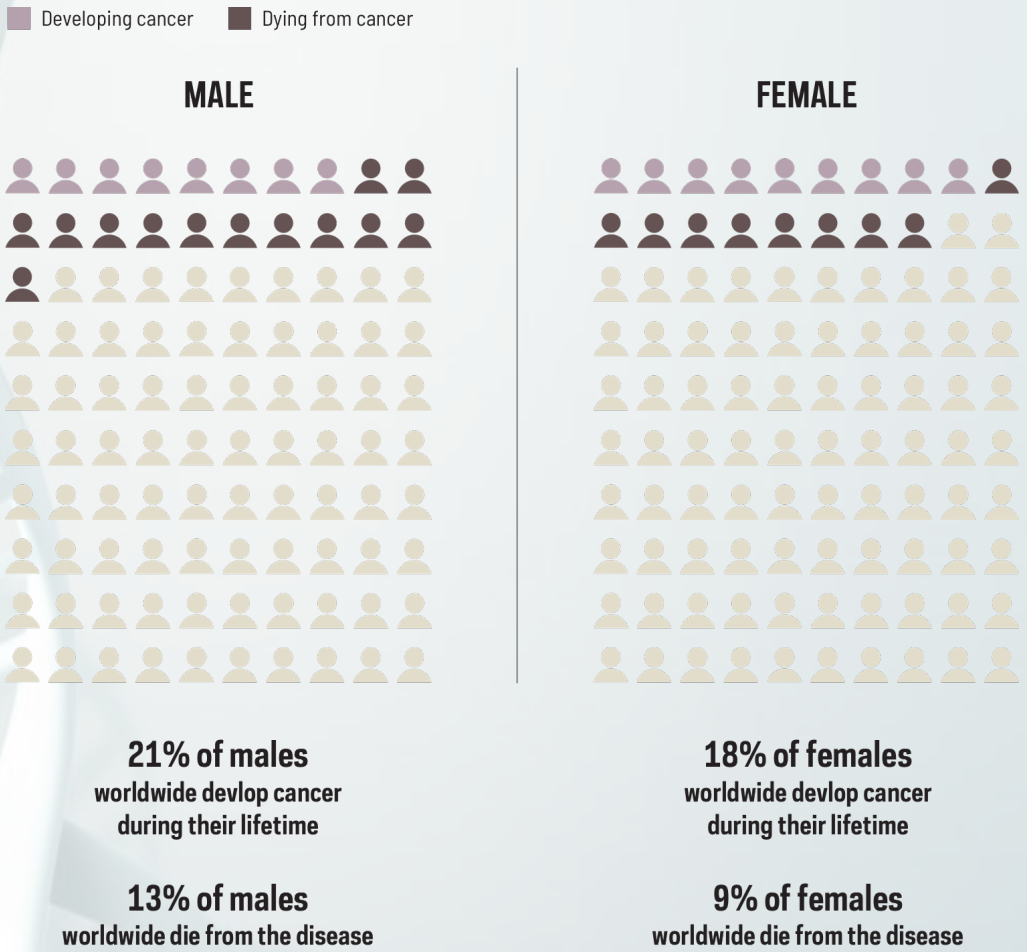


Figure: Porcentaje de casos y muertes por sexo. **Fuente** The Atlas Cancer [2].

Contexto y Motivación

Predicción de nuevos casos

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

Contenido

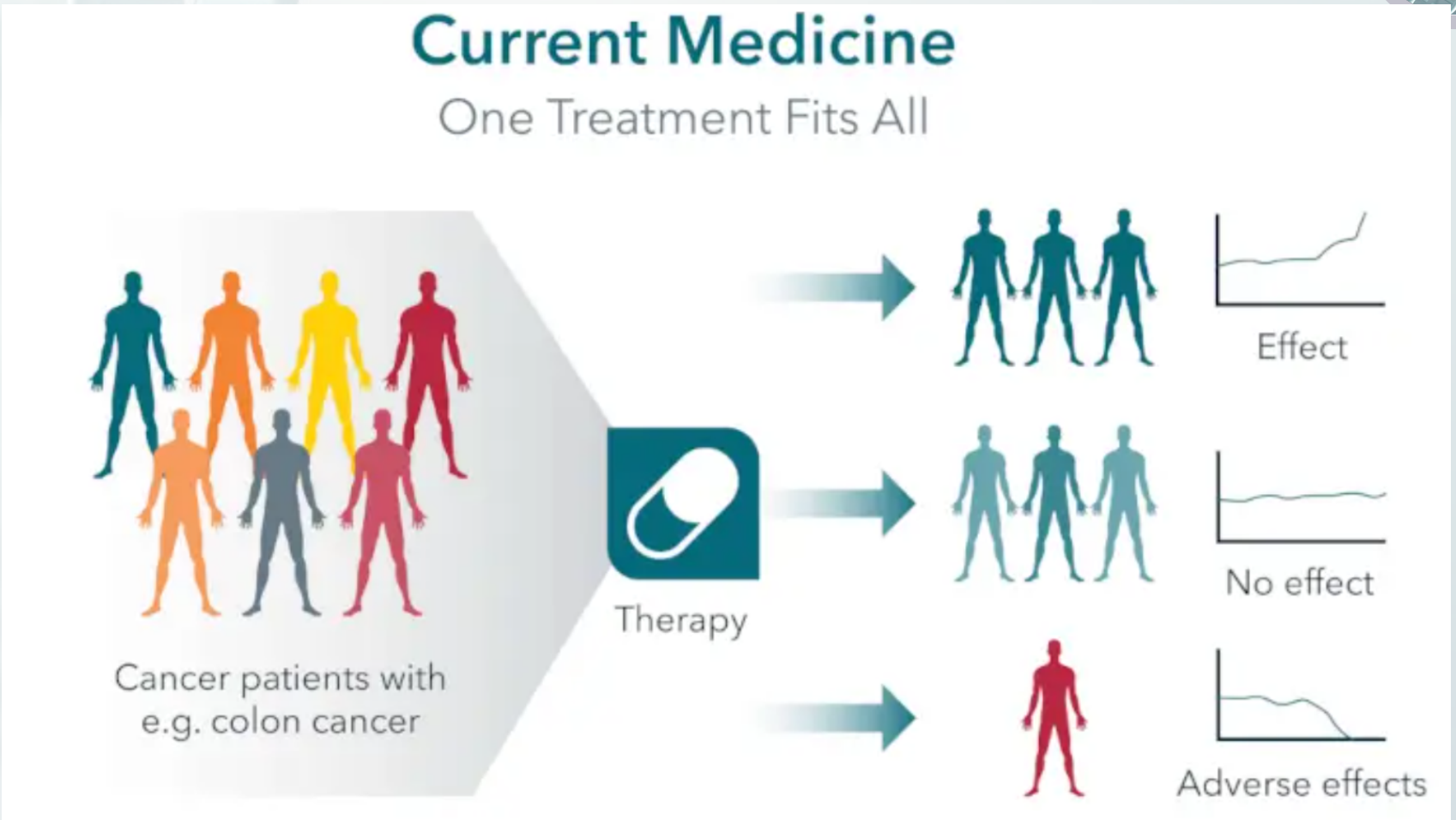


Figure: Pacientes con el mismo tipo de cáncer pueden reaccionar de forma disitinta a los mismos tratamientos. **Fuente** The Atlas Cancer [3].

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].

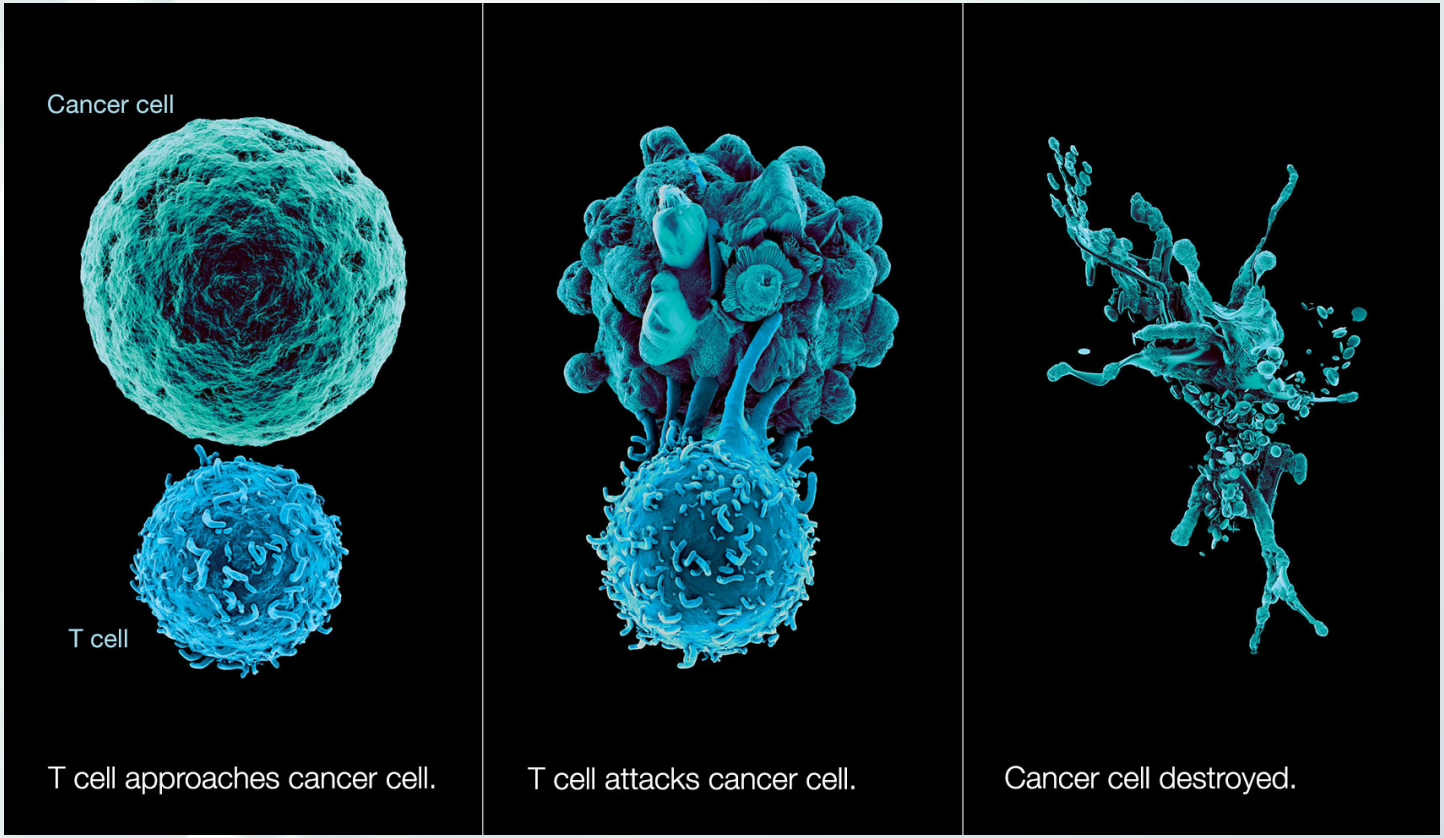


Figure: Ejemplo de como una célula T destruye células del cancer [5].

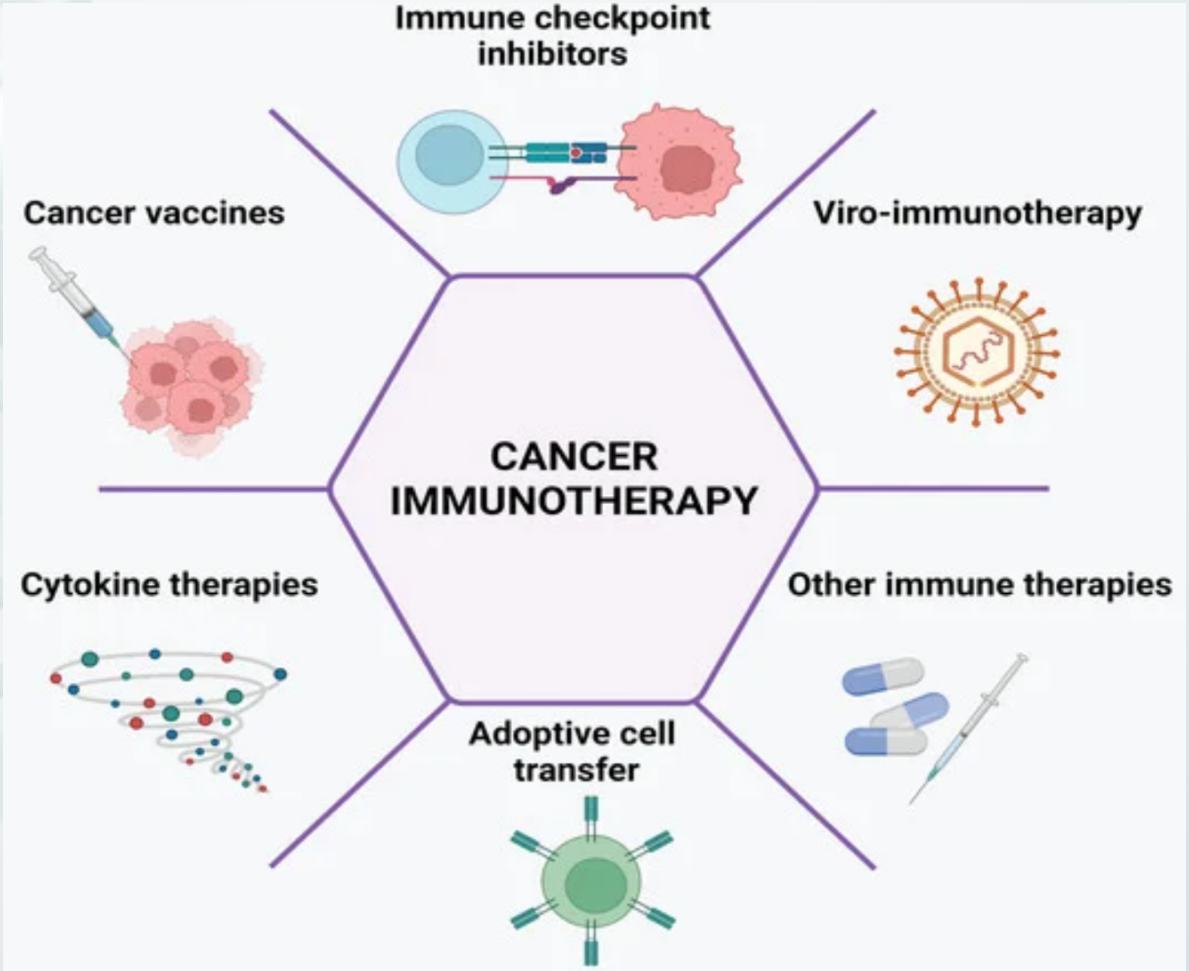


Figure: Tipos de tratamientos para la inmunoterapia del cáncer. **Fuente**: [6].

Contenido

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

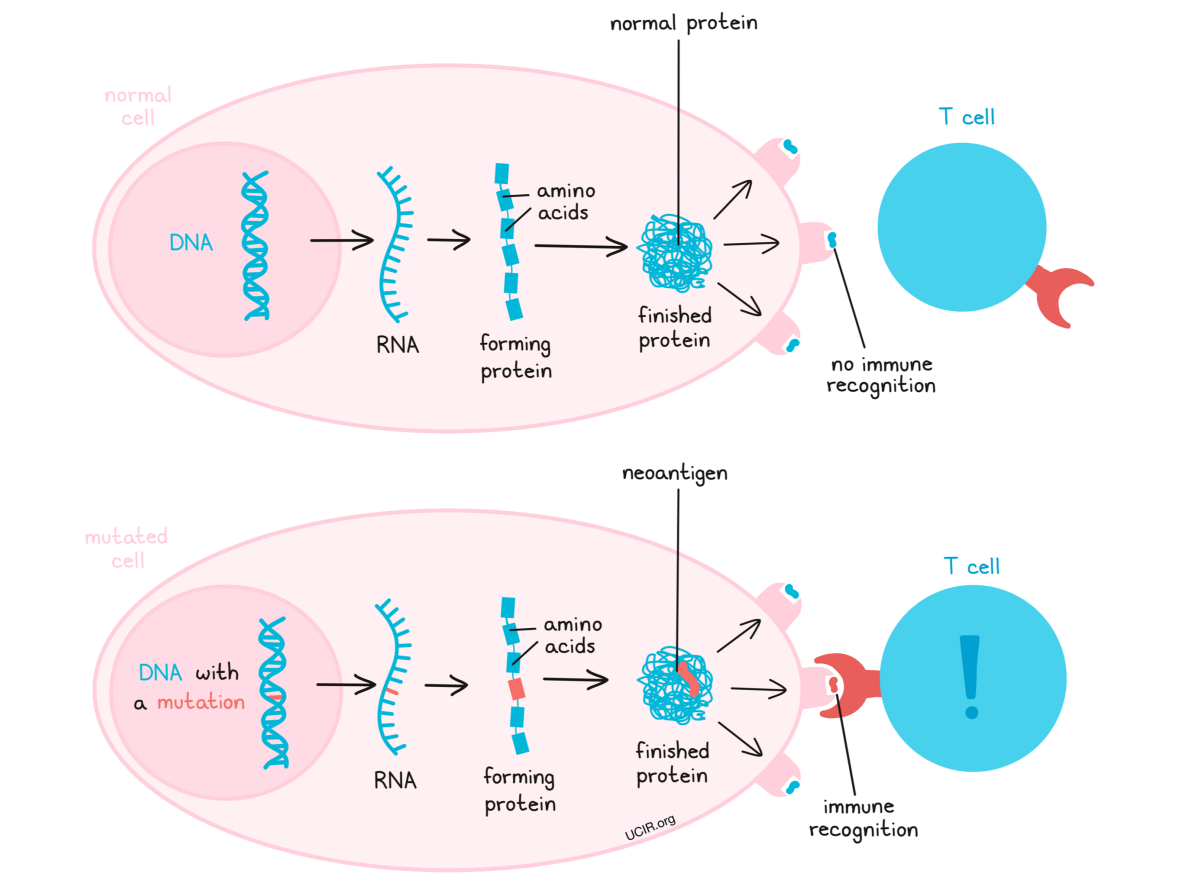


Figure: Neoantígenos y células T. **Fuente**: [9].

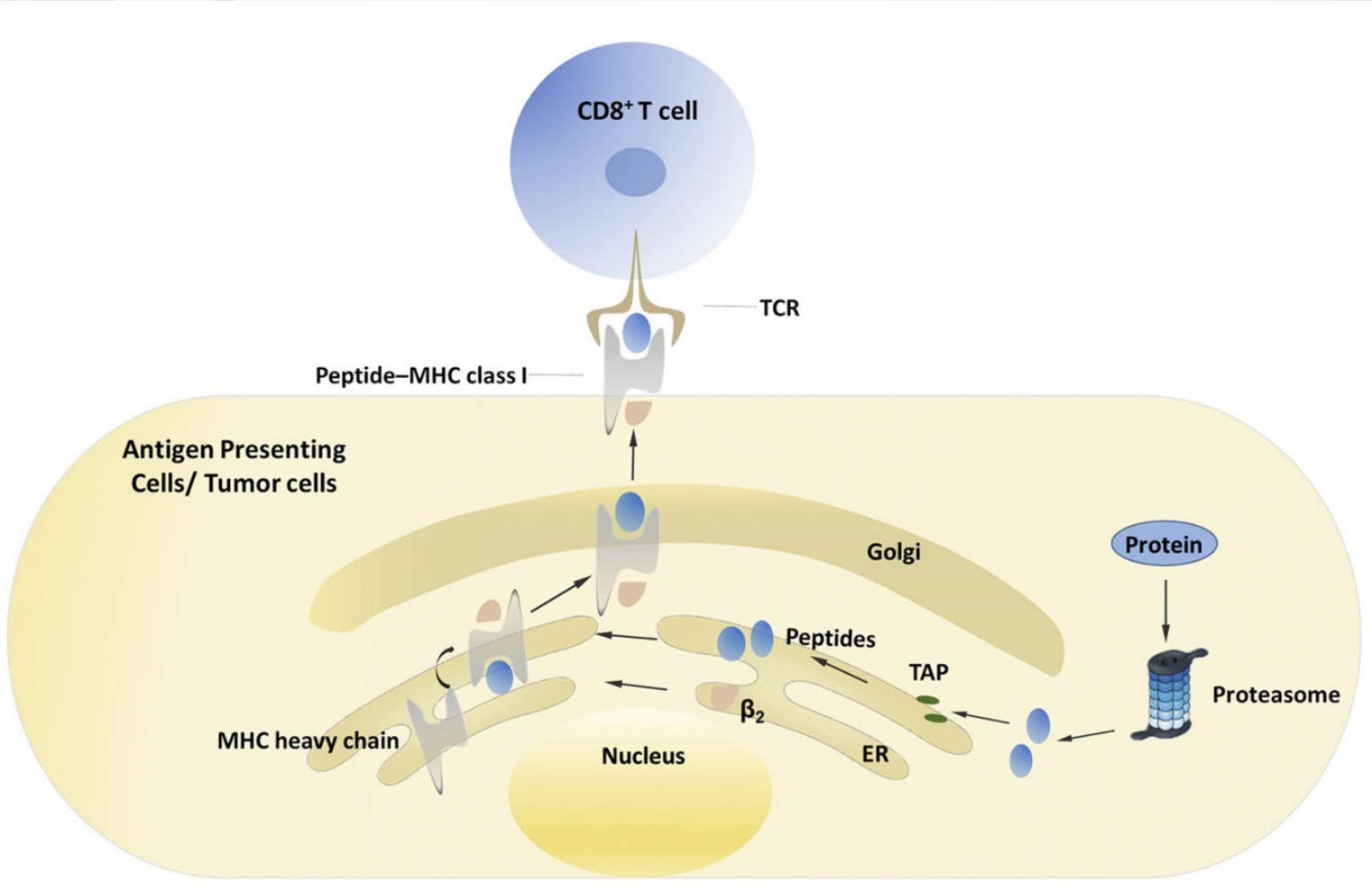


Figure: Presentación de antígenos por MHC-I. Fuente: [10]

Contexto y Motivación
Vacunas personalizadas

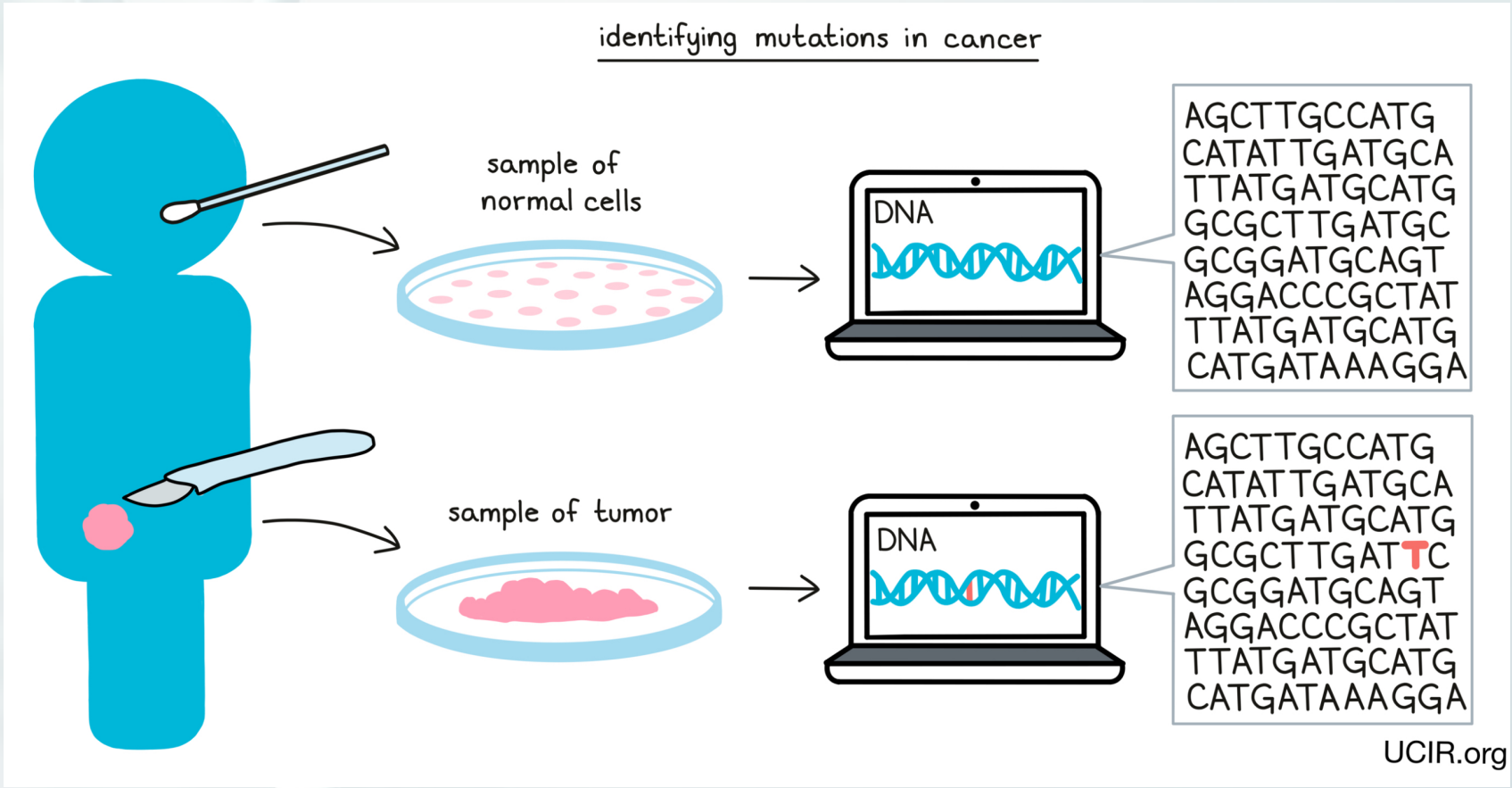
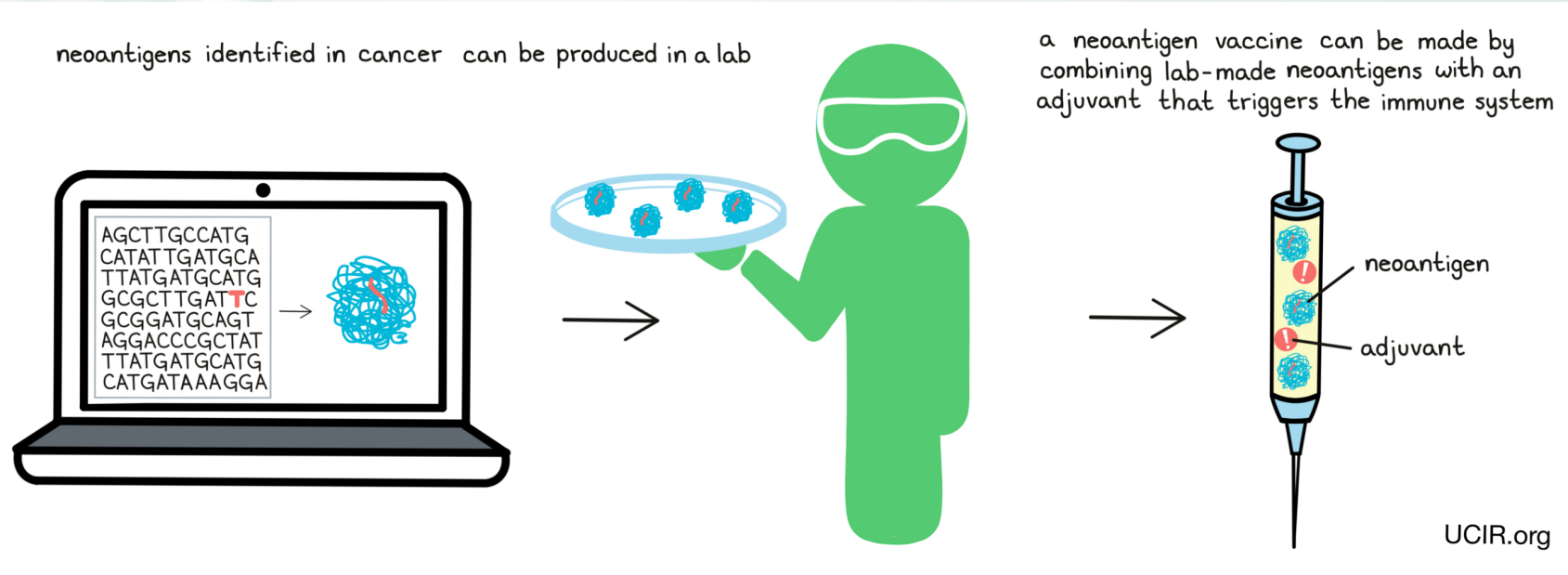


Figure: Proceso para la generación de vacunas contra el cáncer. **Fuente**: [9].



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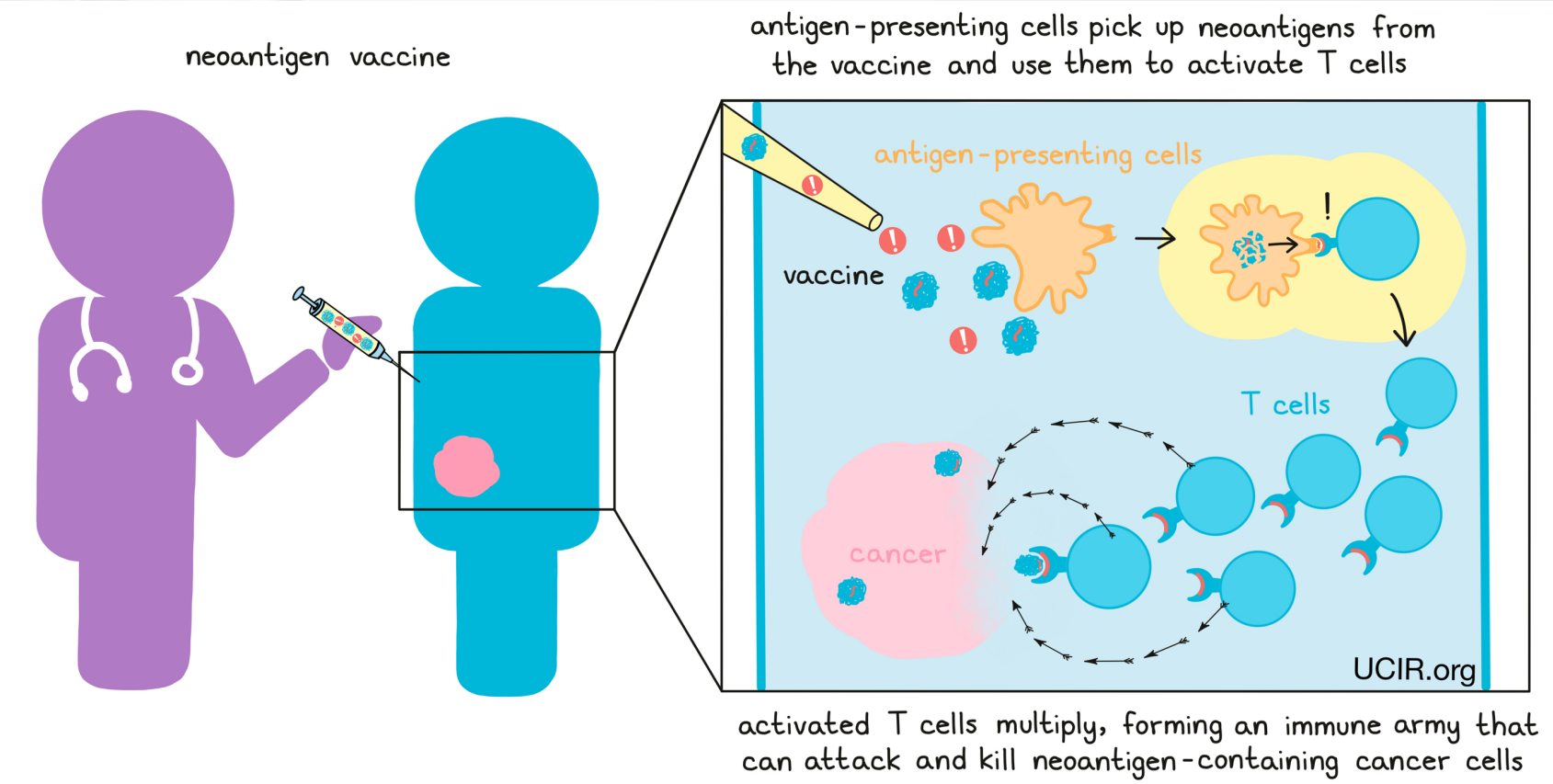

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Contexto y Motivación
Vacunas personalizadas

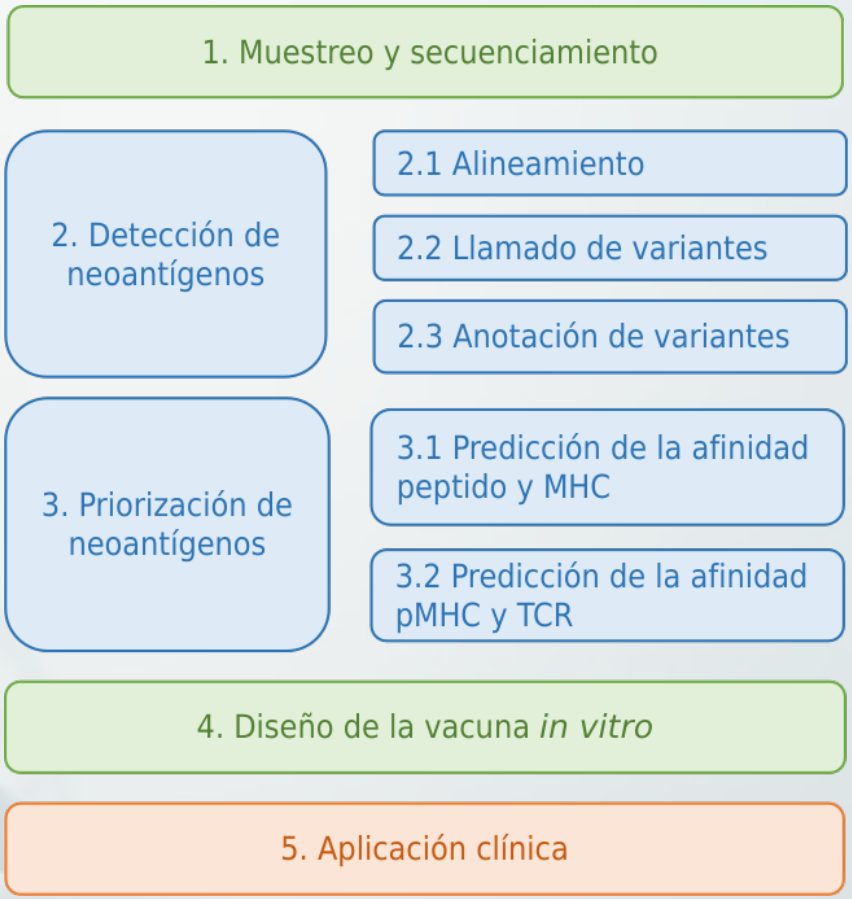


Figure: Resumen del proceso de generación de vacunas contra el cáncer.

Contenido

Problema

Less than 5% of detected neoantigens (peptides binded to MHC) succeed in activating the immune system [12].

This is a **binary classification problem**. A peptide could be represented like: $p = \{A, ..., Q\}$ and a MHC like: $q = \{A, N, ..., Q, E\}$. Finally, we need to know the probability of affinity between p and q (pMHC)

Problema

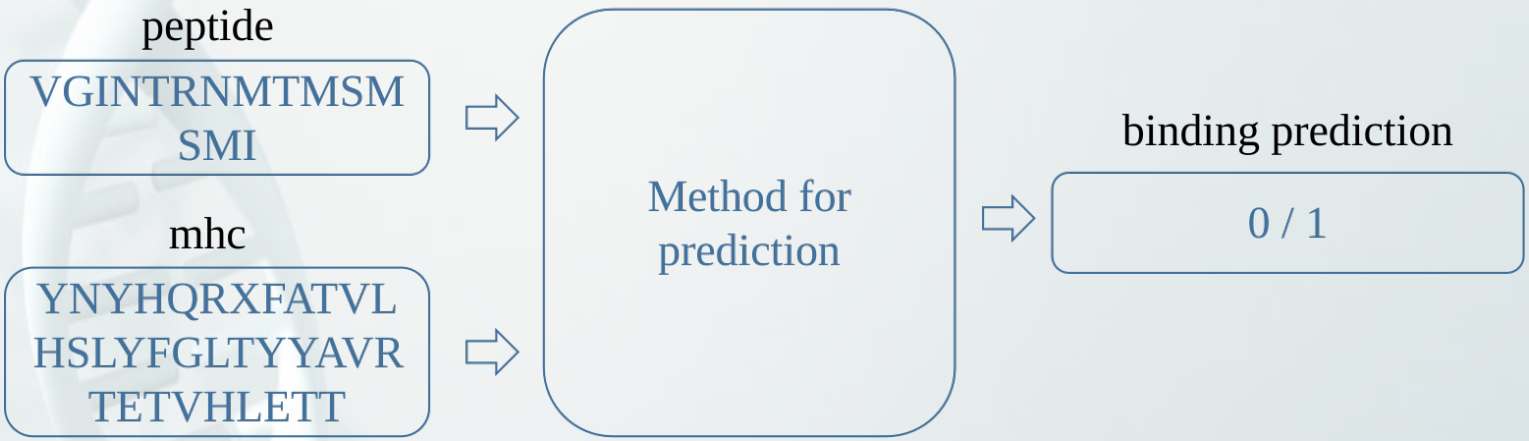


Figure: pMHC binding prediction problem.

Contenido

Proposal

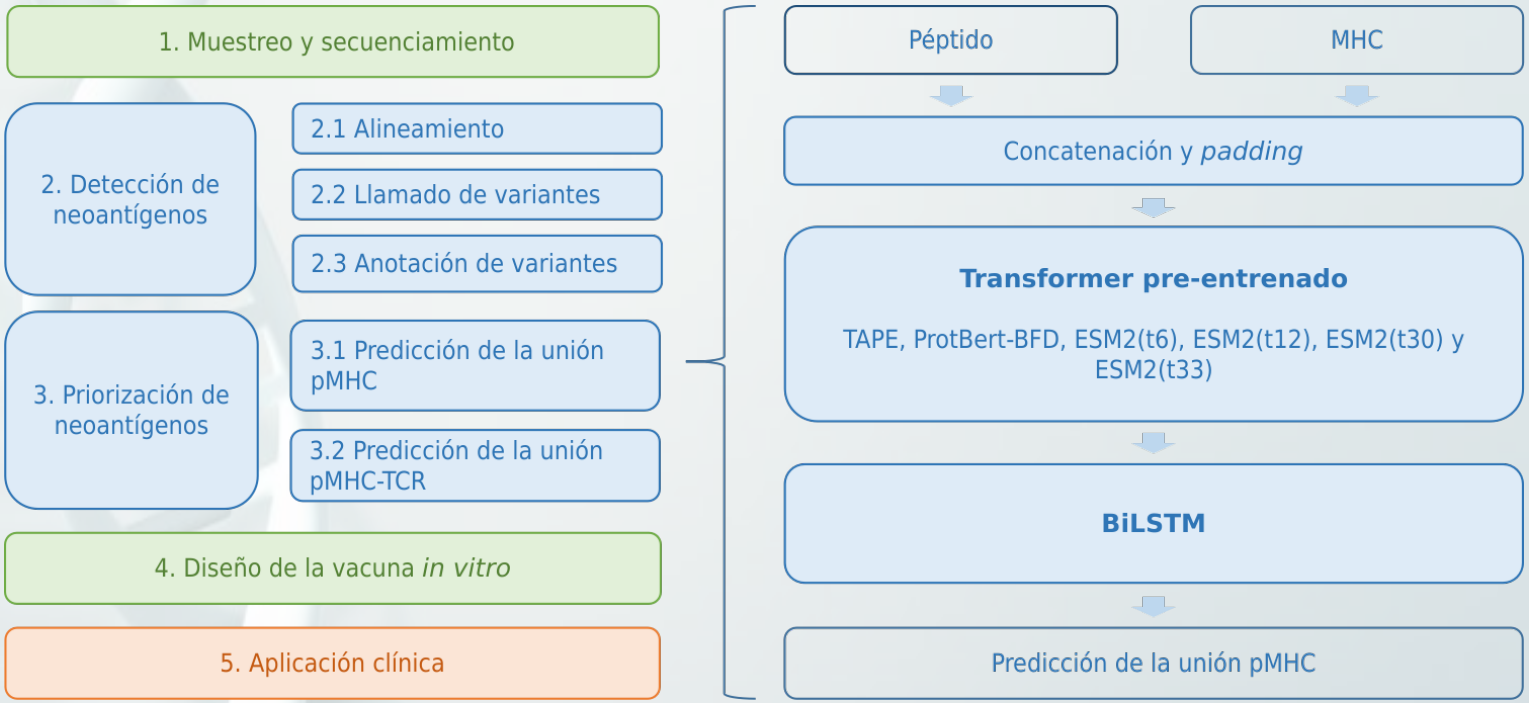


Figure: Proposal for pMHC binding prediction.

Contenido

Databases

Training: 539,019; Validation: 179,673; and Testing: 172,580.

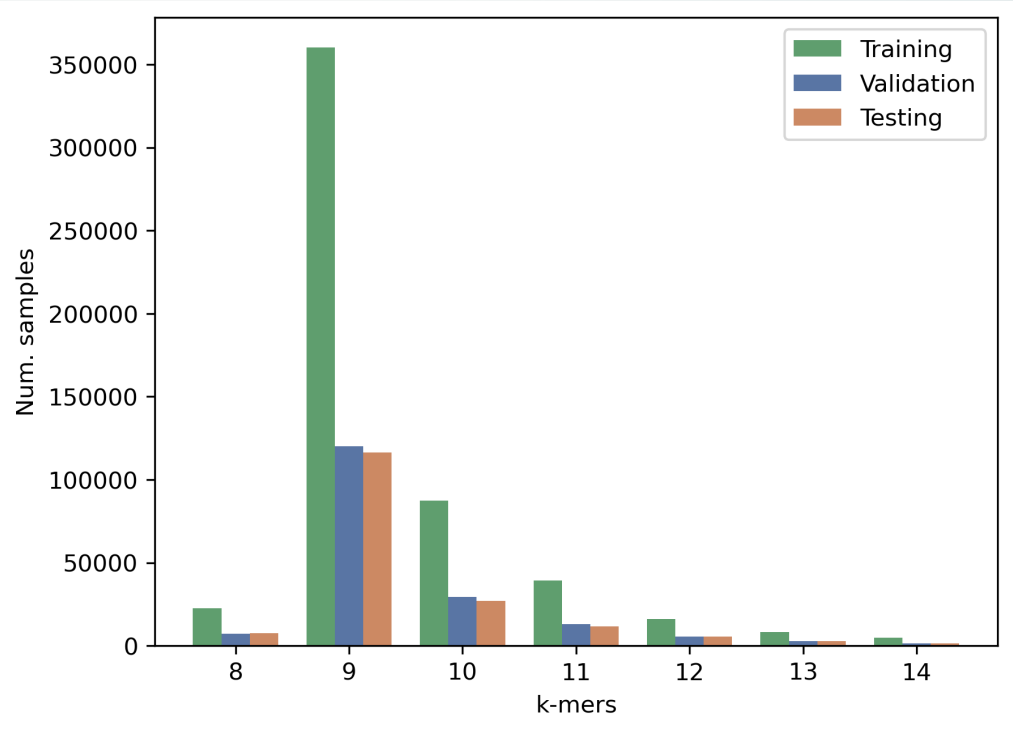


Figure: Number of samples per k-mer.

Contenido

Pre-trained models

Table: Differences between TAPE, ProtBert-DFB, and ESM2. HS: *Hidden size*; AH: *Attention heads*.

Model	BD	Samples	Layers	HS	AH	Params.
TAPE	Pfam	30M	12	768	12	92M
ProtBert-BFD	BFD	2122M	30	1024	16	420M
ESM2(t6)	Uniref50	60M	6	320	20	8M
ESM2(t12)	Uniref50	60M	12	480	20	35M
ESM2(t30)	Uniref50	60M	30	640	20	150M
ESM2(t33)	Uniref50	60M	33	1280	20	650M

Contenido

Results
(Training for 3 epochs)

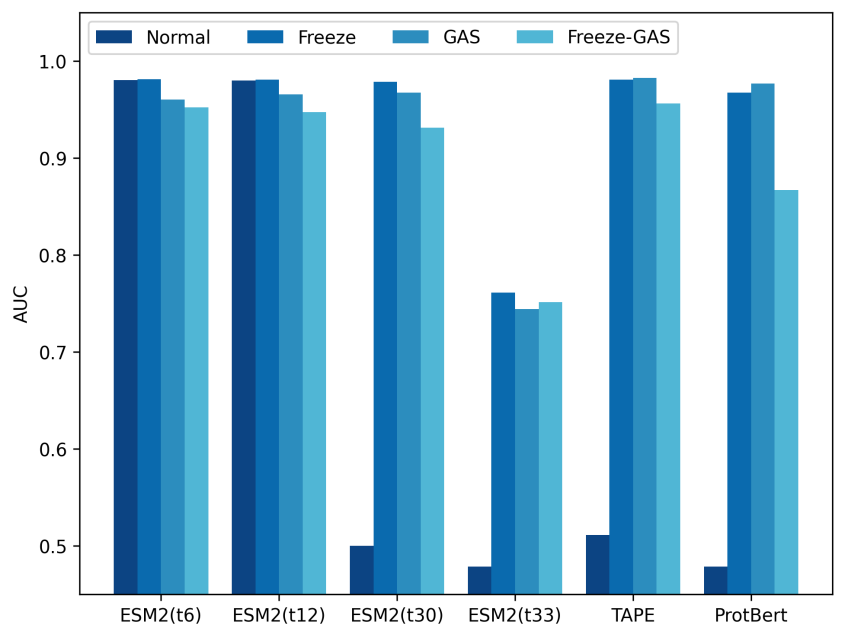
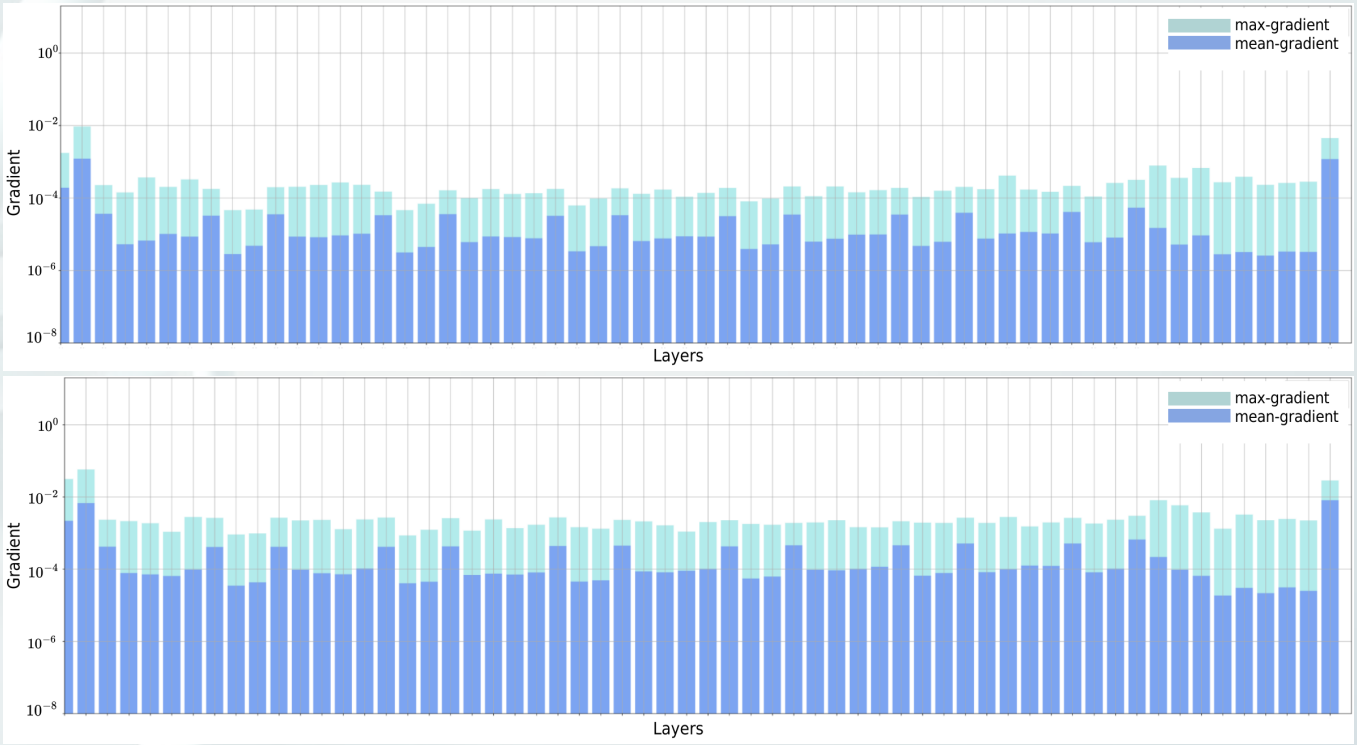


Figure: Comparative analysis of Area Under the Curve (AUC) in Transformer model architectures using various training methodologies.

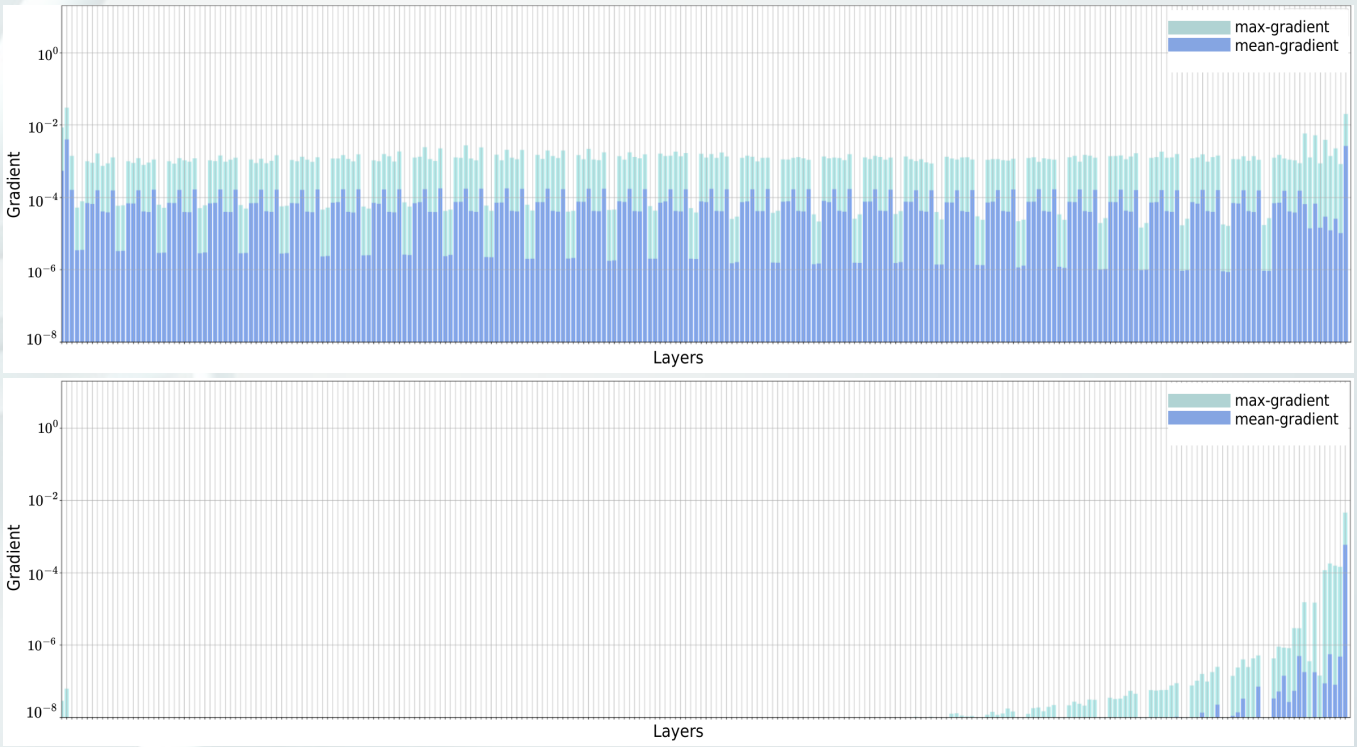
Results
Vanish gradient problem

Gradients for ESM2(t6)



Results
Vanish gradient problem

Gradients for ESM2(t30)



Results

Comparison (Training for 30 epochs)

	Accuracy	Precision	Recall	F1-score	AUC	MCC
ESM2(t6)-Normal	0.9390	0.9333	**0.9453**	0.9392	0.9797	0.8780
ESM2(t6)-Freeze	**0.9401**	**0.9398**	0.9402	**0.9400**	**0.9830**	**0.8802**
ESM2(t6)-GAS	0.9366	0.9322	0.9413	0.9368	0.9818	0.8732
ESM2(t6)-Freeze-GAS	0.9354	0.9326	0.9383	0.9355	0.9813	0.8708
ESM2(t30)-Normal	-	-	-	-	-	-
ESM2(t30)-Freeze	**0.9393**	0.9304	**0.9493**	**0.9397**	0.9787	**0.8787**
ESM2(t30)-GAS	0.9346	**0.9337**	0.9352	0.9345	0.9808	0.8691
ESM2(t30)-Freeze-GAS	0.9363	0.9319	0.9411	0.9365	**0.9818**	0.8726
TAPE-Normal	-	-	-	-	-	-
TAPE-Freeze	0.9395	**0.9404**	0.9382	0.9393	0.9815	0.8790
TAPE-GAS	**0.9415**	0.9352	**0.9484**	**0.9418**	**0.9841**	**0.8831**
TAPE-Freeze-GAS	0.9359	0.9297	0.9428	0.9362	0.9820	0.8719

Results
Comparison with state-of-art tools

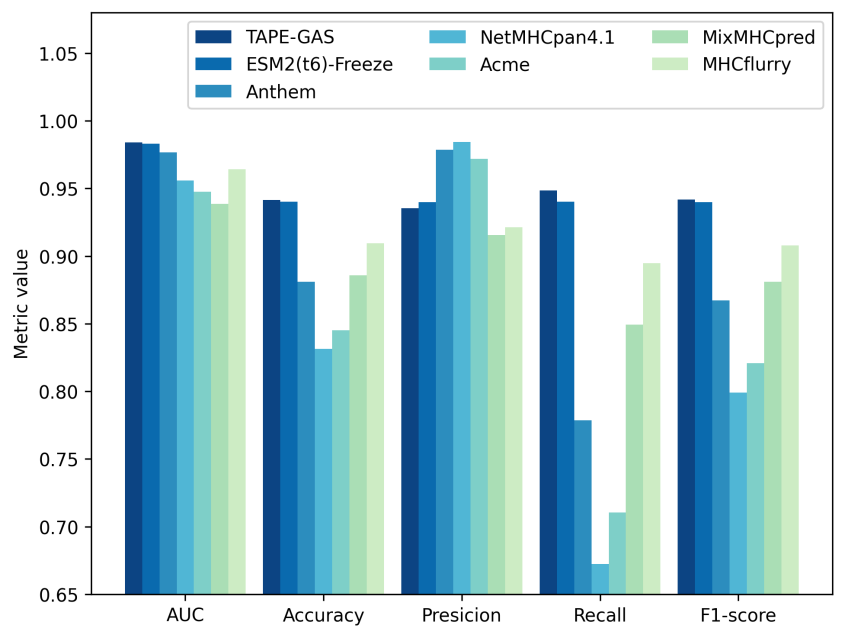


Figure: The AUC values for TAPE-GAS and ESM2(t6) trained for 30 epochs, in comparison to state-of-the-art methods.

Results
Comparison with state-of-art tools

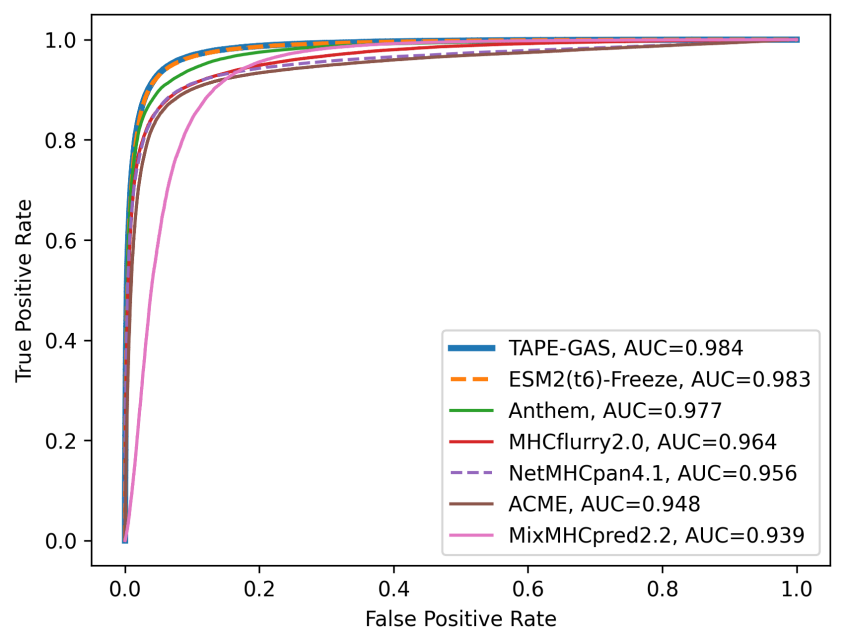


Figure: ROC curves for TAPE-GAS and ESM2(t6) trained for 30 epochs, in comparison to state-of-the-art methods.

Results
Comparison with state-of-art tools

Table: Performance evaluation of Transformer models TAPE-GAS and ESM2(t6)-Freeze, trained for 30 epochs, against Anthem, NetMHCpan4.1, ACME, MixMHCpred2.2, and MhcFlurry2.0.

	Accuracy	Precision	Recall	F1-score	AUC	MCC
TAPE-GAS	**0.9415**	0.9352	**0.9484**	**0.9418**	**0.9841**	**0.8831**
ESM2(t6)-Freeze	**0.9401**	0.9398	**0.9402**	**0.9400**	**0.9830**	**0.8802**
Anthem	0.8811	**0.9786**	0.7787	0.8673	0.9768	0.7785
NetMHCpan4.1	0.8312	**0.9844**	0.6724	0.7991	0.9557	0.6982
ACME	0.8452	0.9717	0.7105	0.8208	0.9476	0.7165
MixMHCpred2.2	0.8857	0.9155	0.8493	0.8811	0.9386	0.7733
MhcFlurry2.0	0.9093	0.9211	0.8948	0.9078	0.9642	0.8189

Contenido

Discussion

Fine-tuning ESM2 models

The most favorable results were obtained with the smallest model, **ESM2(t6)**. we believe is not sufficiently large for ESM2(t33), a model boasting 650 million parameters.

Another potential reason could be attributed to the use of **Rotary Position Embedding (RoPE)** used instead of absolute positional encoding.

Discussion

Layer Freezing and GAS

This approach involves locking the Transformer model while updating only the BiLSTM parameters. This method is generally well-suited to accelerate the training process, even though it may lead to a slight sacrifice in performance.

Surprisingly, **for ESM2 models, this methodology yielded the best results, while for TAPE and ProtBert-BFD, it yielded the expected outcomes**.

Discussion

TAPE, ProtBert-BFD and ESM2

ProtBert-BFD got the worst result despite this model were pre-trained with the largest dataset BFD with 2122M samples. We believe, this result is caused by the noisy information and sequence mistakes in BFD dataset.

TAPE achieved the best results. TAPE models were pre-trained using the Pfam dataset, it is derived from UniProtKB and **selectively includes sequences belonging to Reference Proteomes rather than the entire UniProtKB**

ESM2(t6) achieved results that closely rival TAPE. ESM2(t6) comprises only 8 million parameters, compared to 92 million parameters of TAPE.

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