TERAPIAS AVANZADAS EN EL CANCER: PAPEL DE LA INMUNOTERAPIA ADOPTIVA EN NEOPLASIAS HEMATOLÓGICAS Y SÓLIDAS

Diploma de Experto
en Medicina Personalizada y de Precisión

PANMEP

Tumores sólidos

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Consejería de Salud y Consumo

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OBJETIVOS DE APRENDIZAJE

- Introducción a la inmunidad (inmunidad innata y adaptativa)
- Sinapsis inmunológica, transducción de señales de activación
- Sistema inmunitario y cáncer. Estrategias de inmunoterapia
- Terapia celular adoptiva, conceptos generales
- Tumores sólidos: dinámica del crecimiento tumoral
- Microambiente tumoral: efecto sobre el sistema inmunitario
- Estrategias de optimización de las inmunoterapias

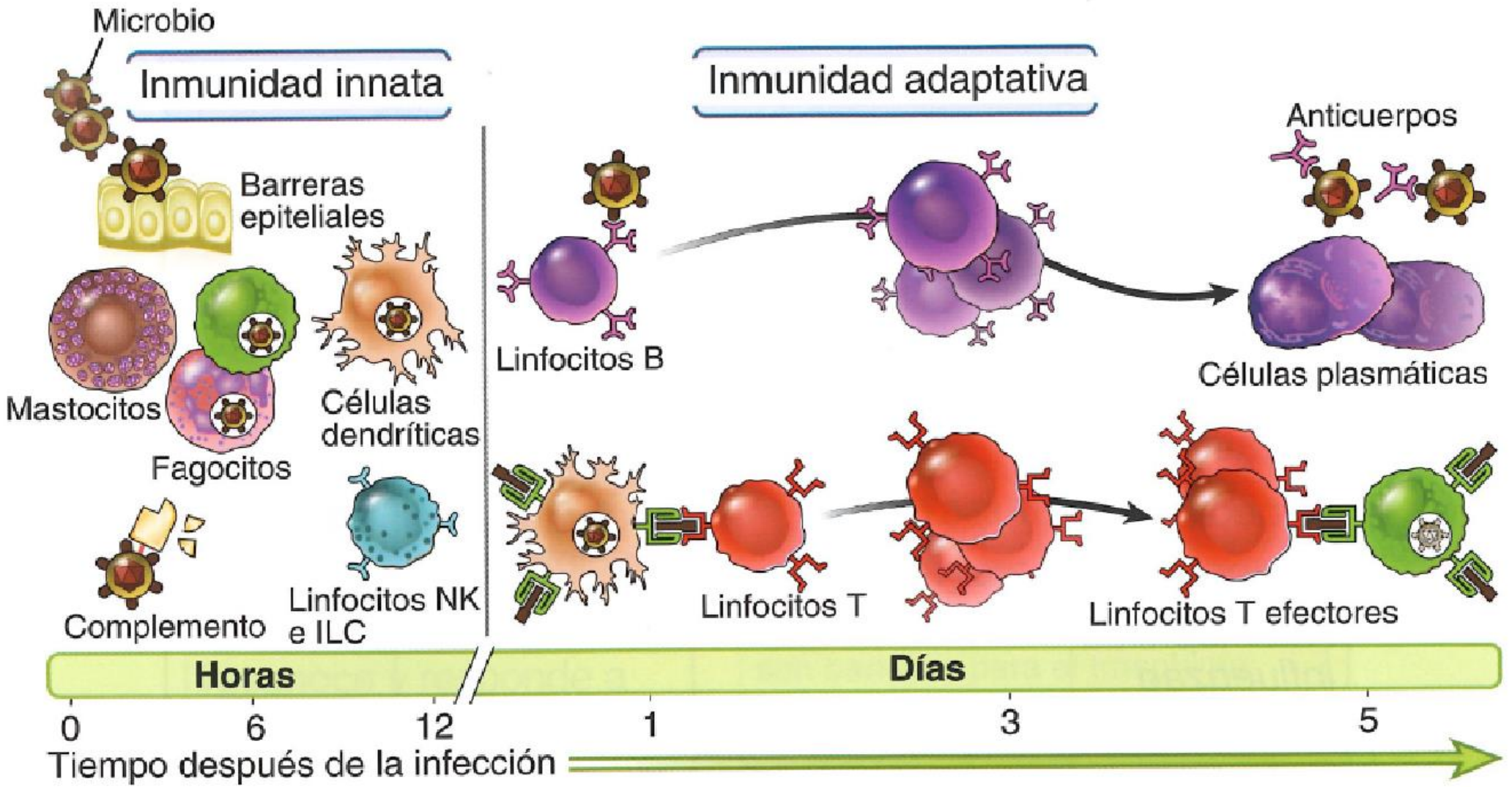
COMPONENTES DE LA INMUNIDAD

Inmunidad innata: grupo de mecanismos de resistencia a la enfermedad que no son específicos de un antígeno particular

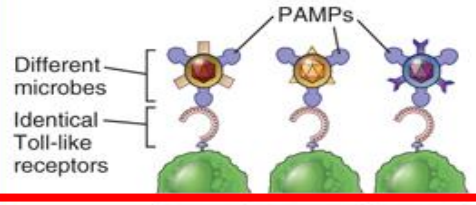
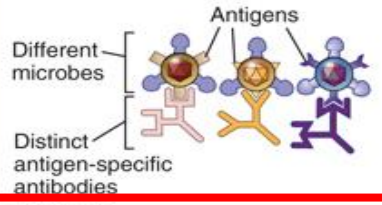
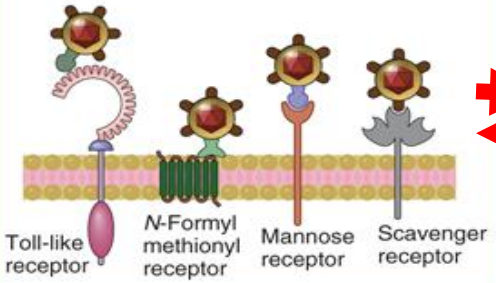
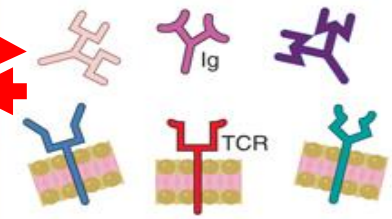
Inmunidad adaptativa. Muestran un alto grado de especificidad y una capacidad de memoria

- Especificidad antigénica
- Diversidad
- Memoria inmunológica
- Discriminación de lo propio y de lo extraño

Respuesta inmunitaria

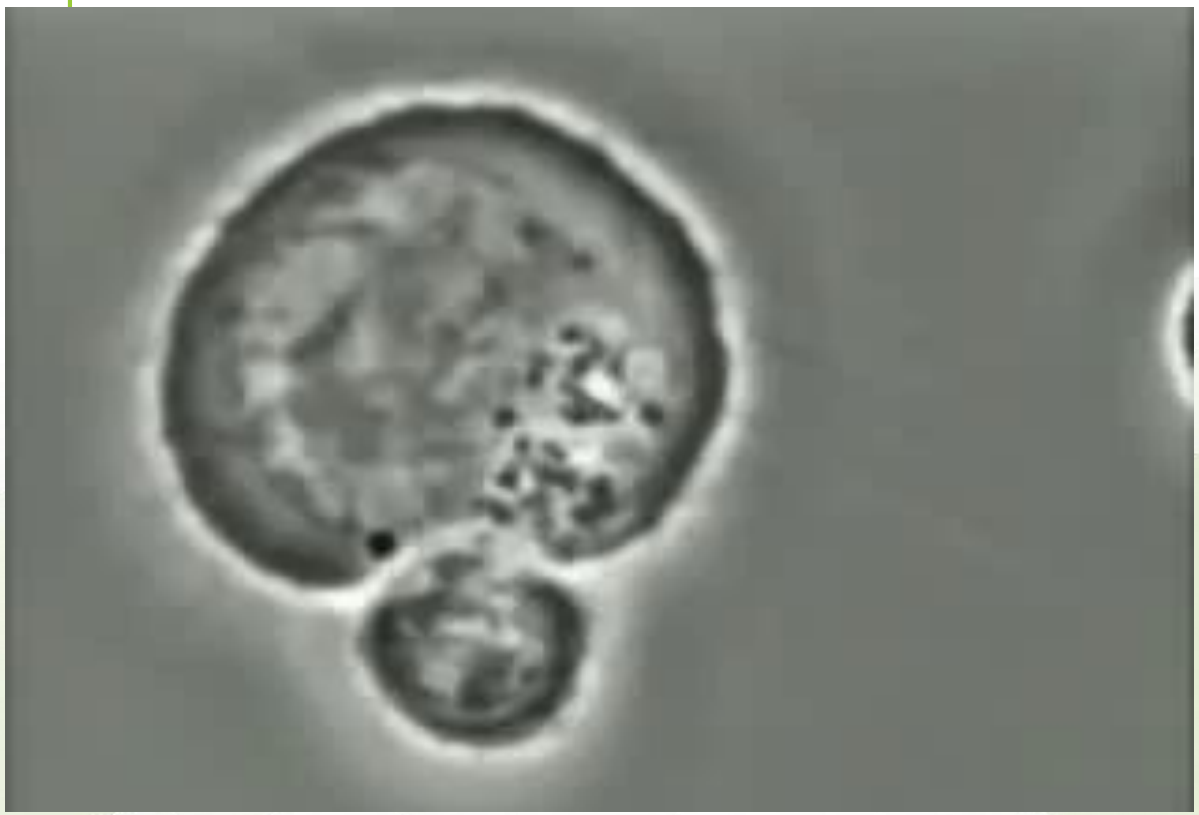


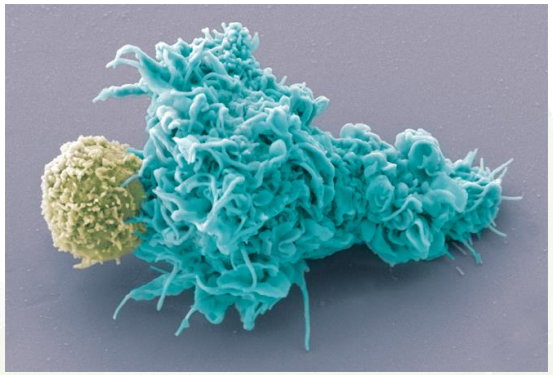
Especificidad y receptores de la inmunidad innata e inmunidad adaptativa

Feature	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Number of microbial molecules recognized	About 1000 molecular patterns (estimated)	>10^7 antigens
Receptors	Encoded in germline; limited diversity (pattern recognition receptors) 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Number and types of receptors	<100 different types of invariant receptors	Only 2 types of receptors (Ig and TCR), with millions of variations of each
Distribution of receptors	Nonclonal: Identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Genes encoding receptors	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (hence the possibility of autoimmunity)

Abbas , Litchman and Pober

Sinapsis inmunológica y rutas de señalización





Outer ring (red) pSMAC	Inner circle (green) cSMAC
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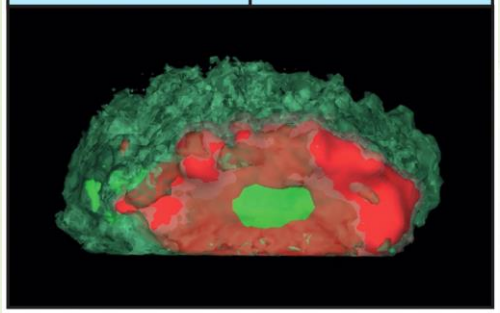
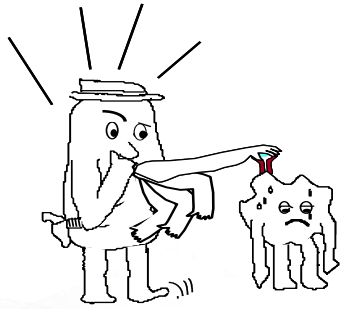


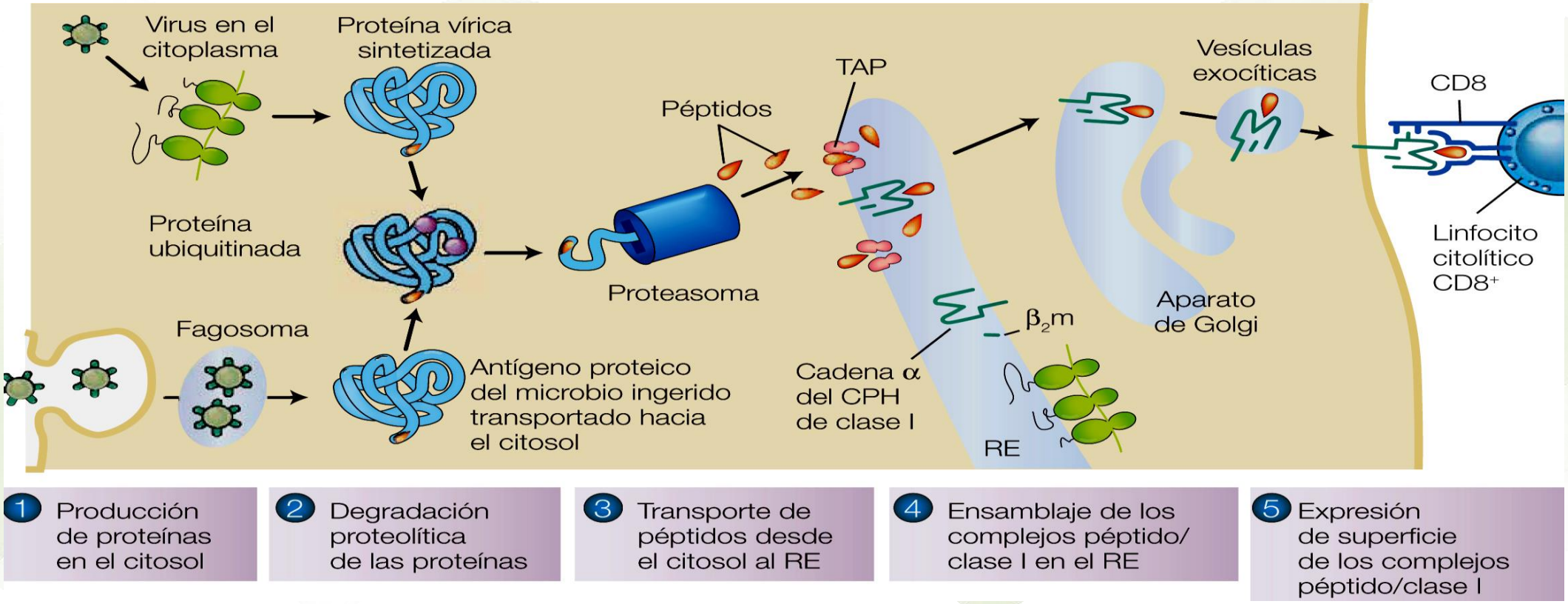
Figure 8-30 Immunobiology, 6/e. (© Garland Science 2005)

¿QUÉ VEN LOS LINFOCITOS T ANTITUMORALES?



La vía de presentación citosólica.

Ag intracelular



Adaptado de Abbas et al, Cell and Molec Immunol 6th Ed

Revisado en Leone P et al. JNCI J Natl Cancer Inst 2013;105:1172-1187

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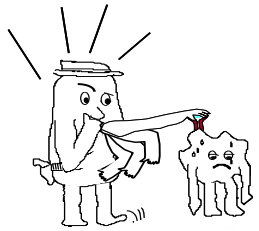
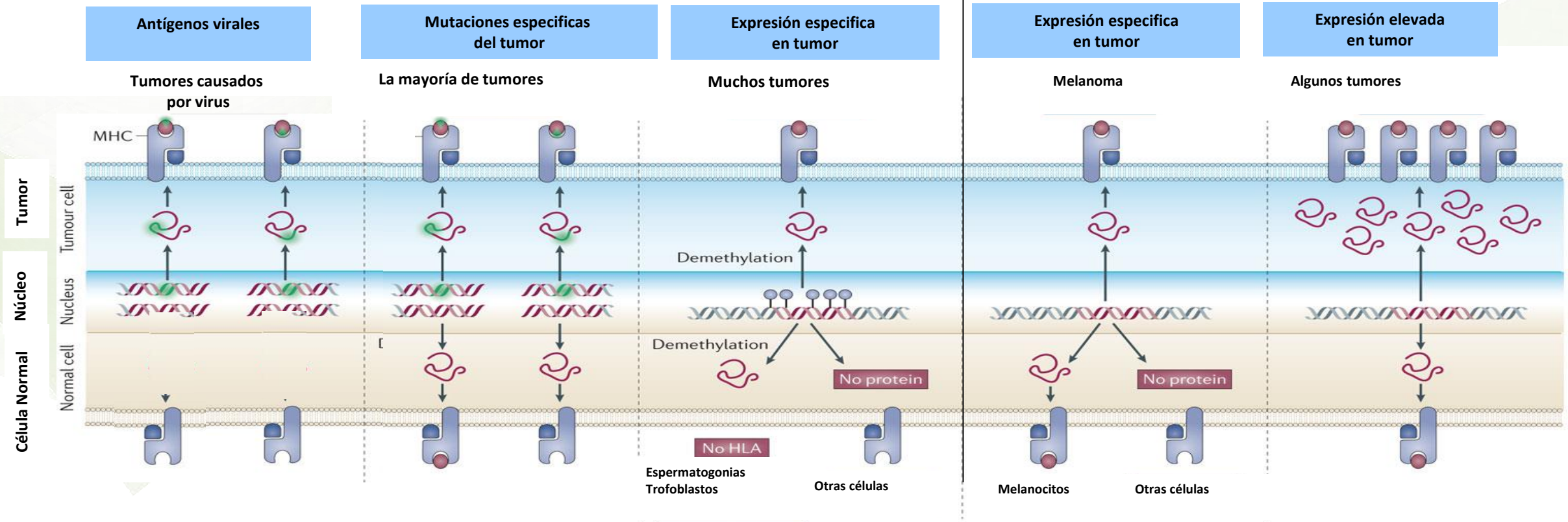


1. Antígenos con alta especificidad tumoral

2. Antígenos con baja especificidad tumoral



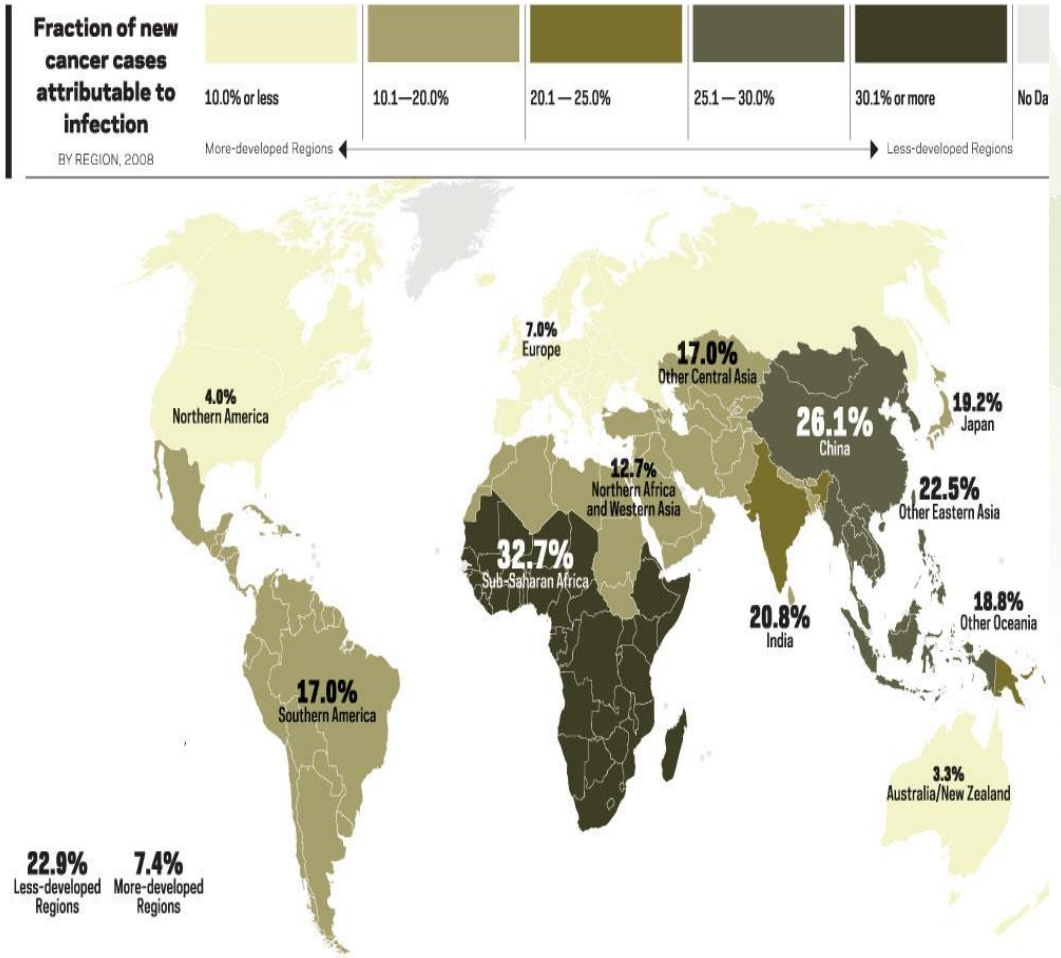
Modificado de Coulie et al. Nature Reviews Cancer (2014) 14, 135–146

Antígenos virales:

Datos globales de los cánceres atribuibles a infecciones en 2008

≈ 16.1% de los cánceres son atribuibles a agentes infecciosos

22.9% en países en desarrollo
7.4 % en países desarrollados
3.3% en Australia
32.7 en África sub-Sahariana

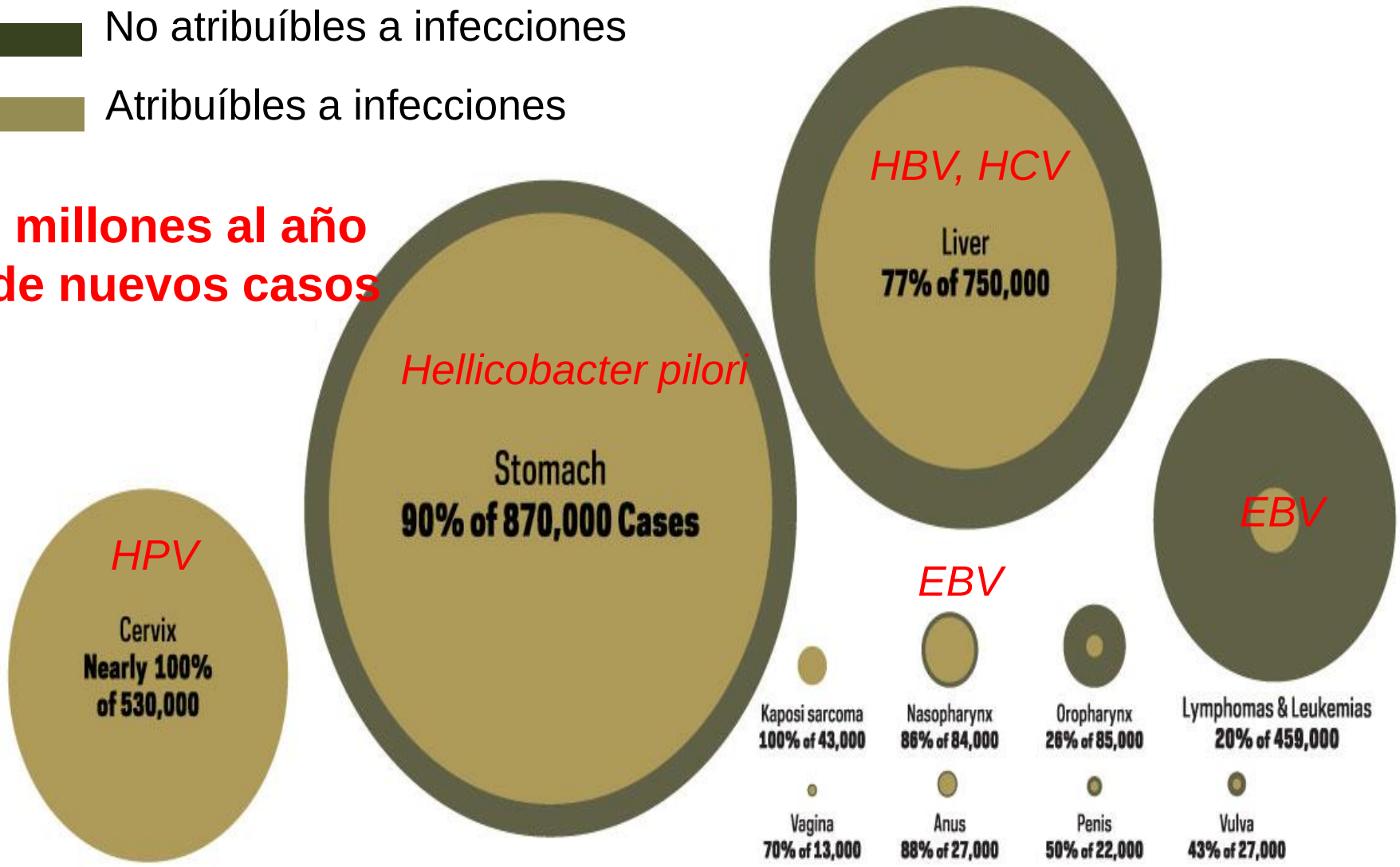


Muchos de los cánceres más comunes son atribuibles a infecciones.
% de nuevos casos de cáncer causados por infección

No atribuíbles a infecciones

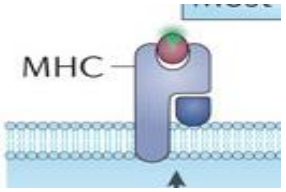
Atribuíbles a infecciones

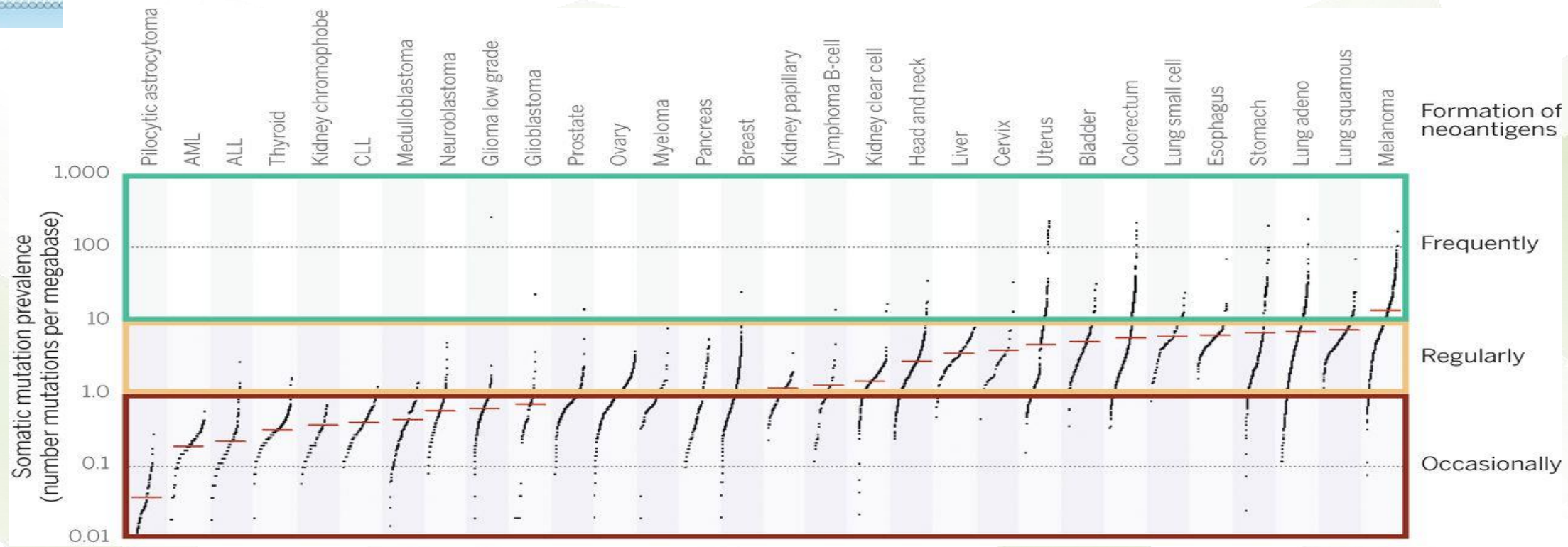
2 millones al año de nuevos casos



The cancer atlas

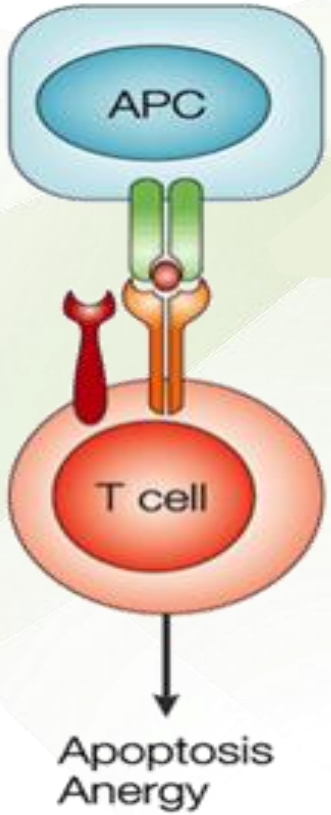
Carga mutacional en cánceres humanos: estimación del repertorio de neoantígenos





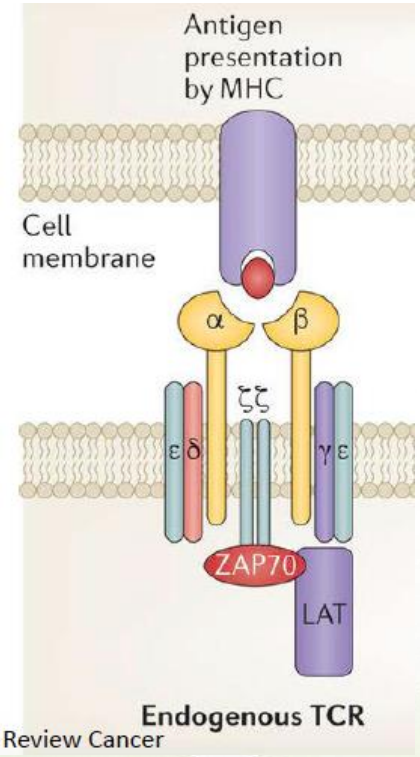
Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74
Coulie et al. Nature Reviews Cancer (2014) 14, 135–146
Alexandrov et al, Nature, 2013.

LA COESTIMULACIÓN EN LA ACTIVACIÓN LINFOCITARIA

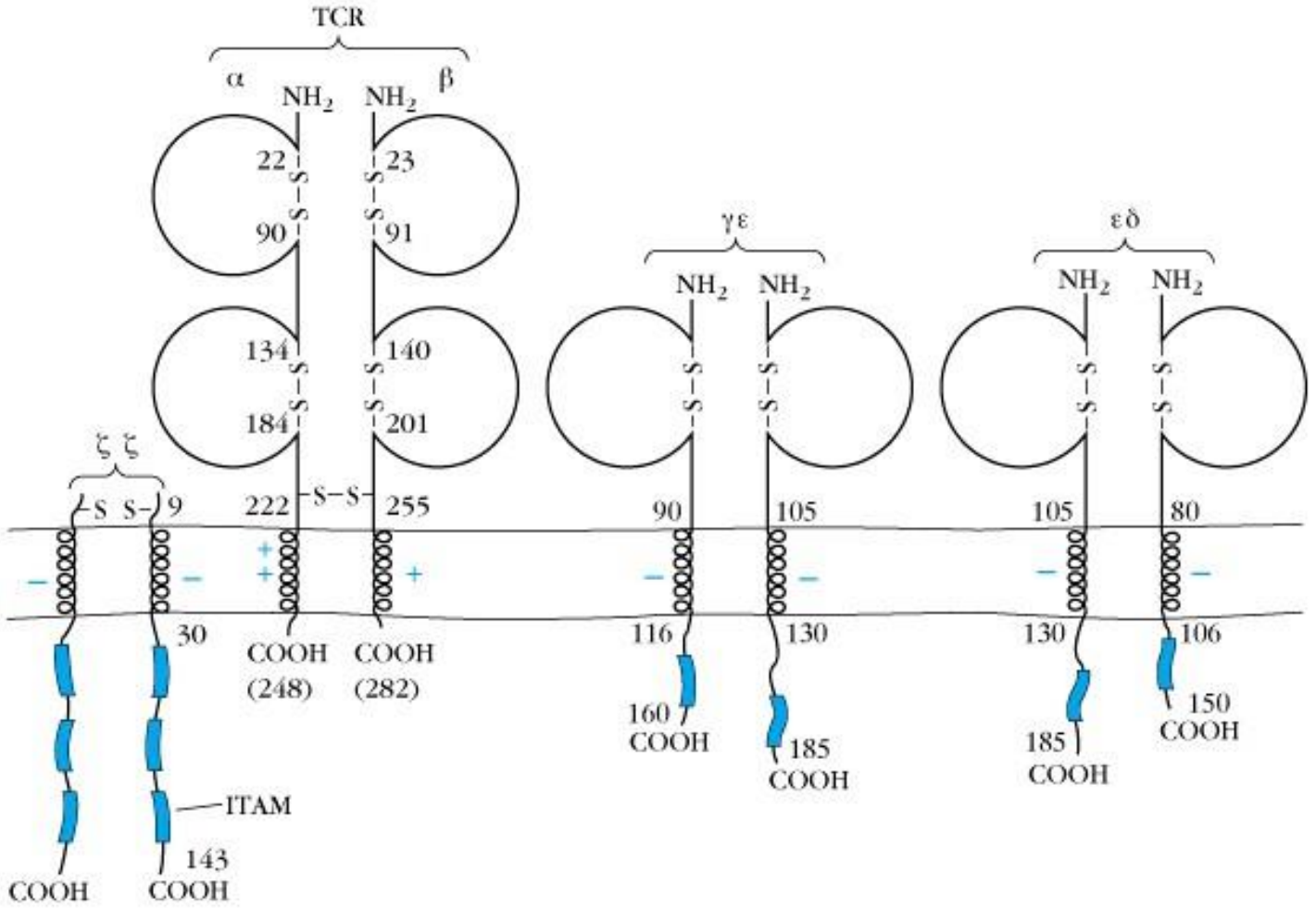


*Alegre, Nature Reviews Immunology **1**, 220-228, 2001*

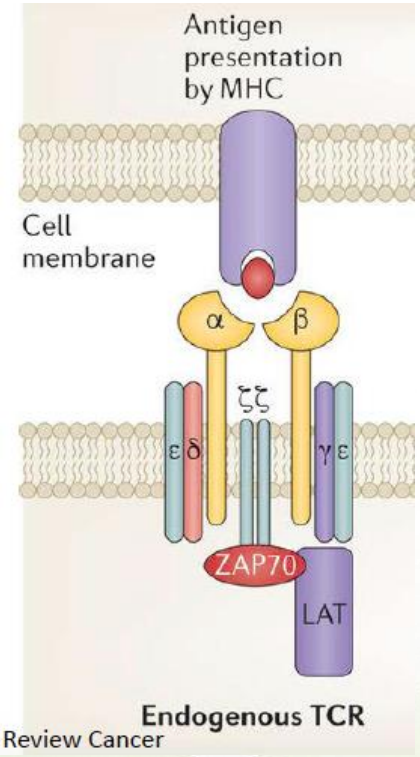
Complejo CD3-TCR



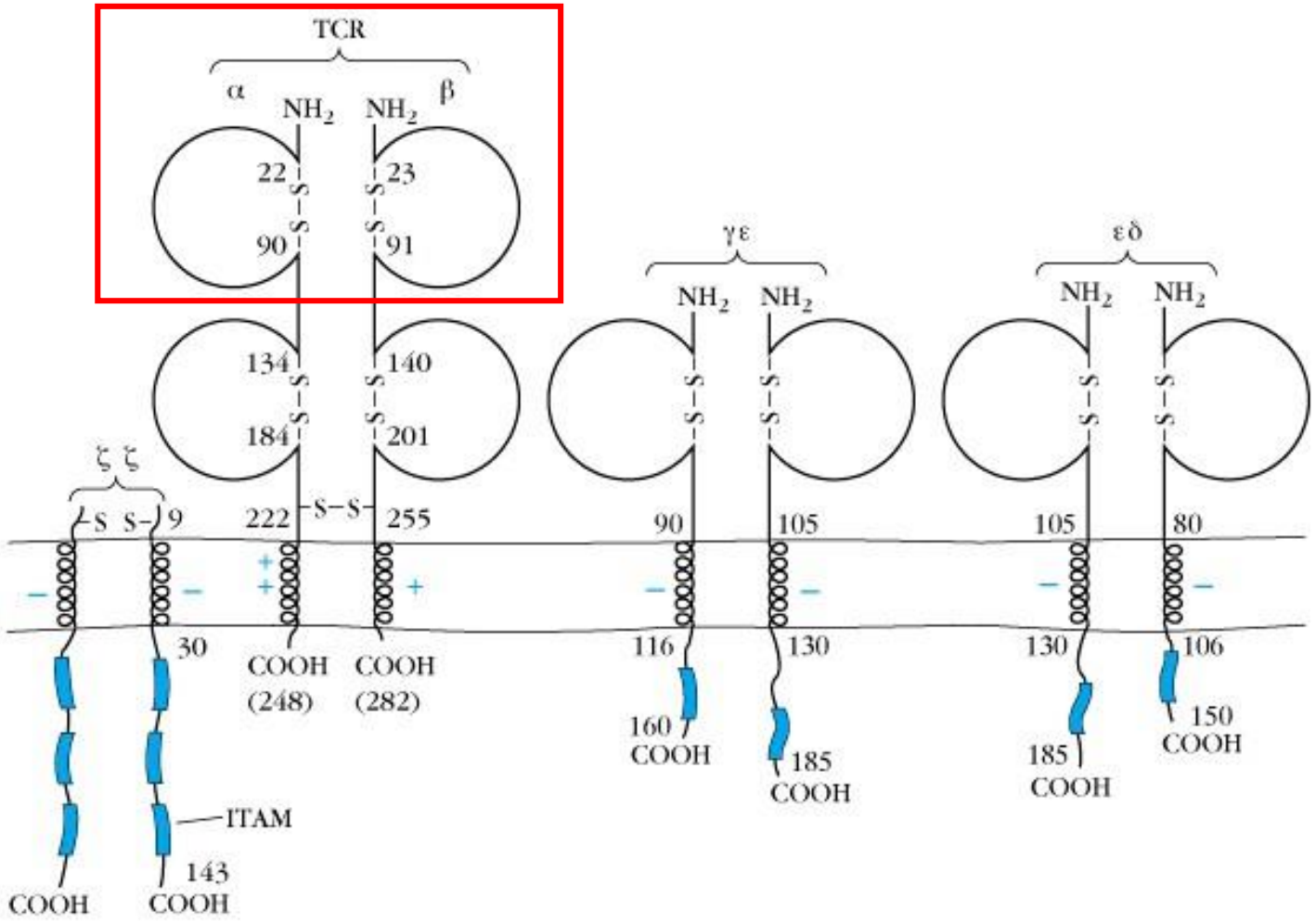
Review Cancer



Complejo CD3-TCR:reconocimiento de Ag

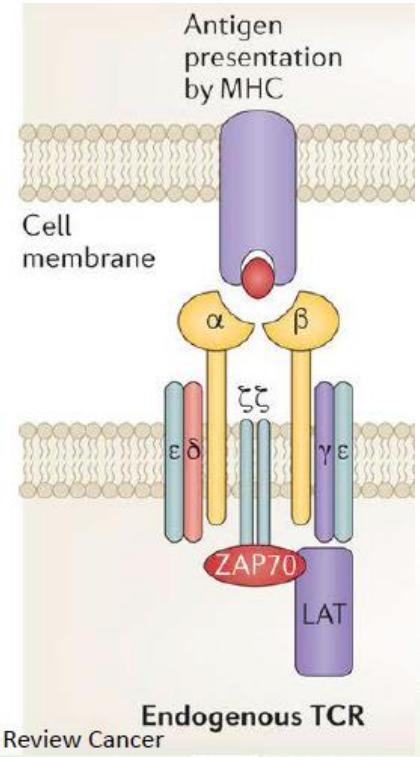


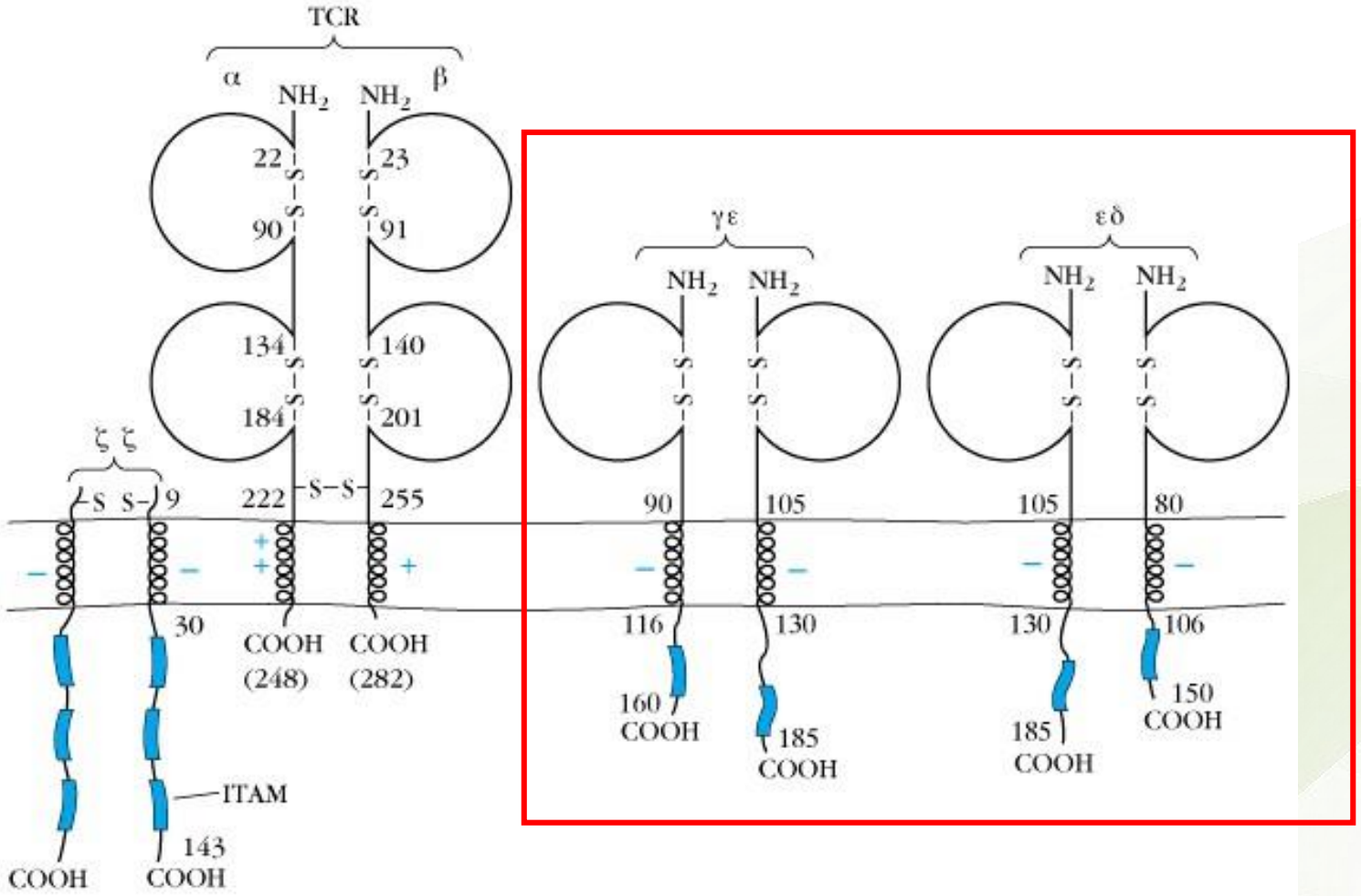
Review Cancer



Las cadenas α y β reconocen el Ag en moléculas MHC

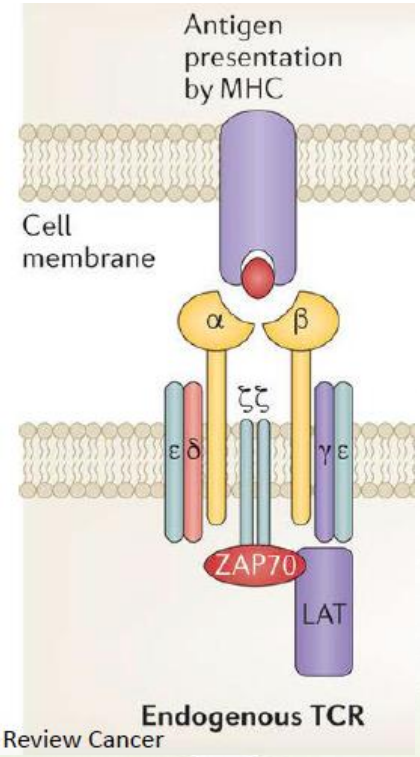
Complejo CD3-TCR

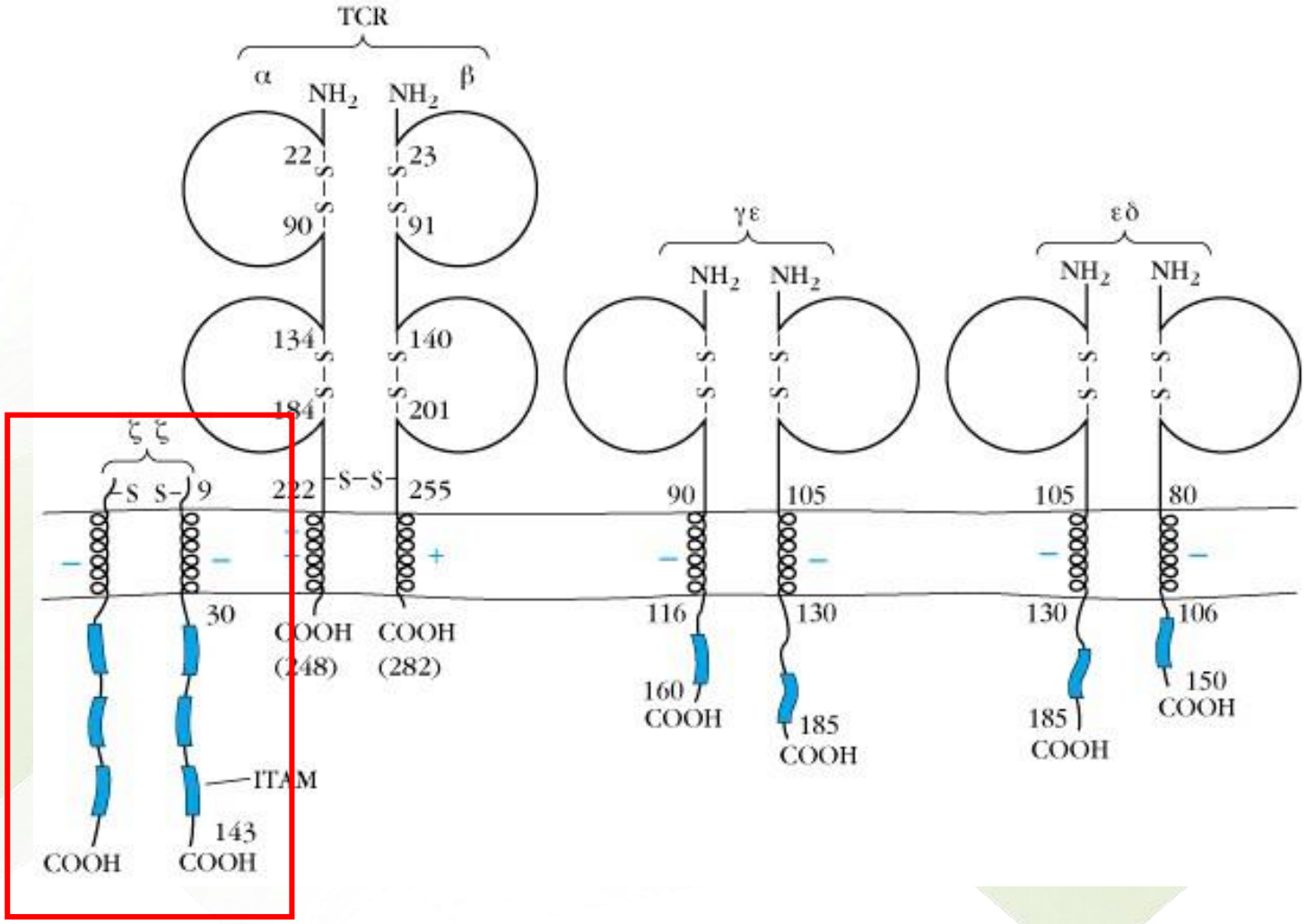




El complejo CD3 está constituido por tres moléculas: γ, δ y ε

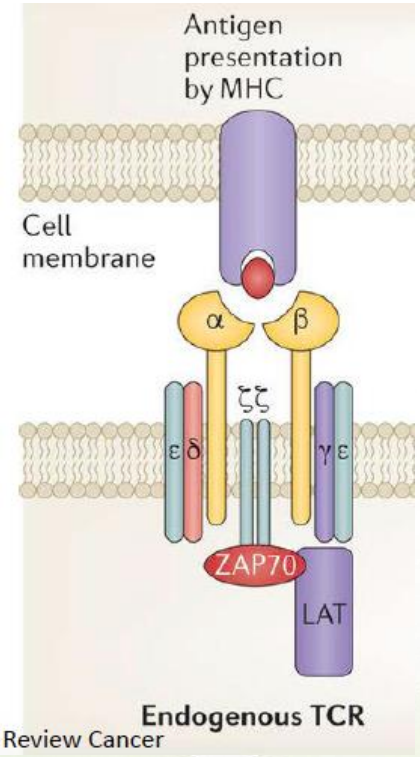
Complejo CD3-TCR

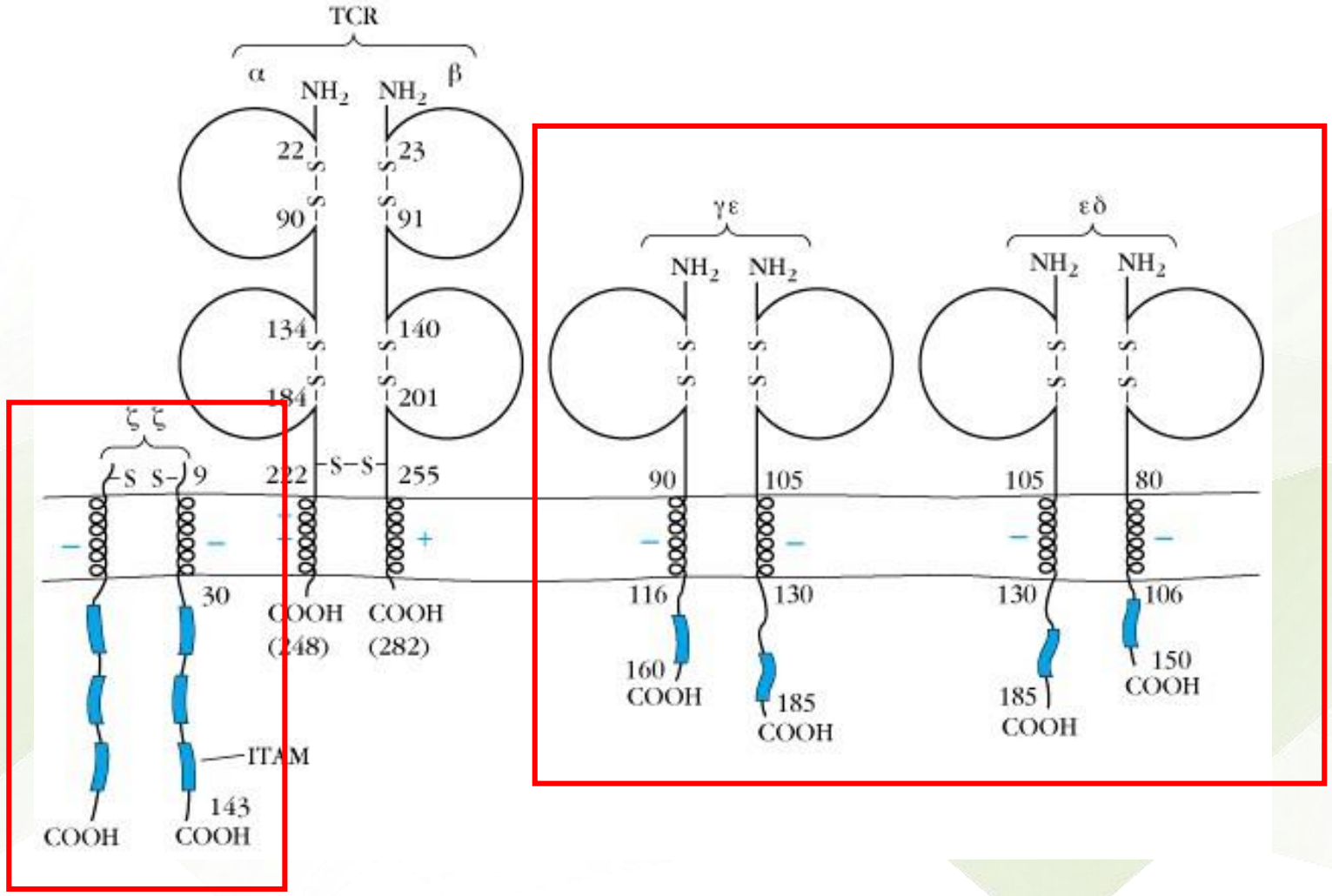




La cadena ζ es un homodímero con una región extracelular de 9-aa.

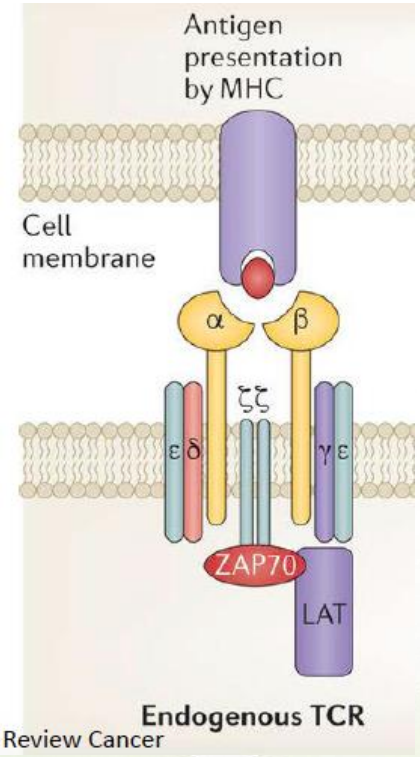
Complejo CD3-TCR

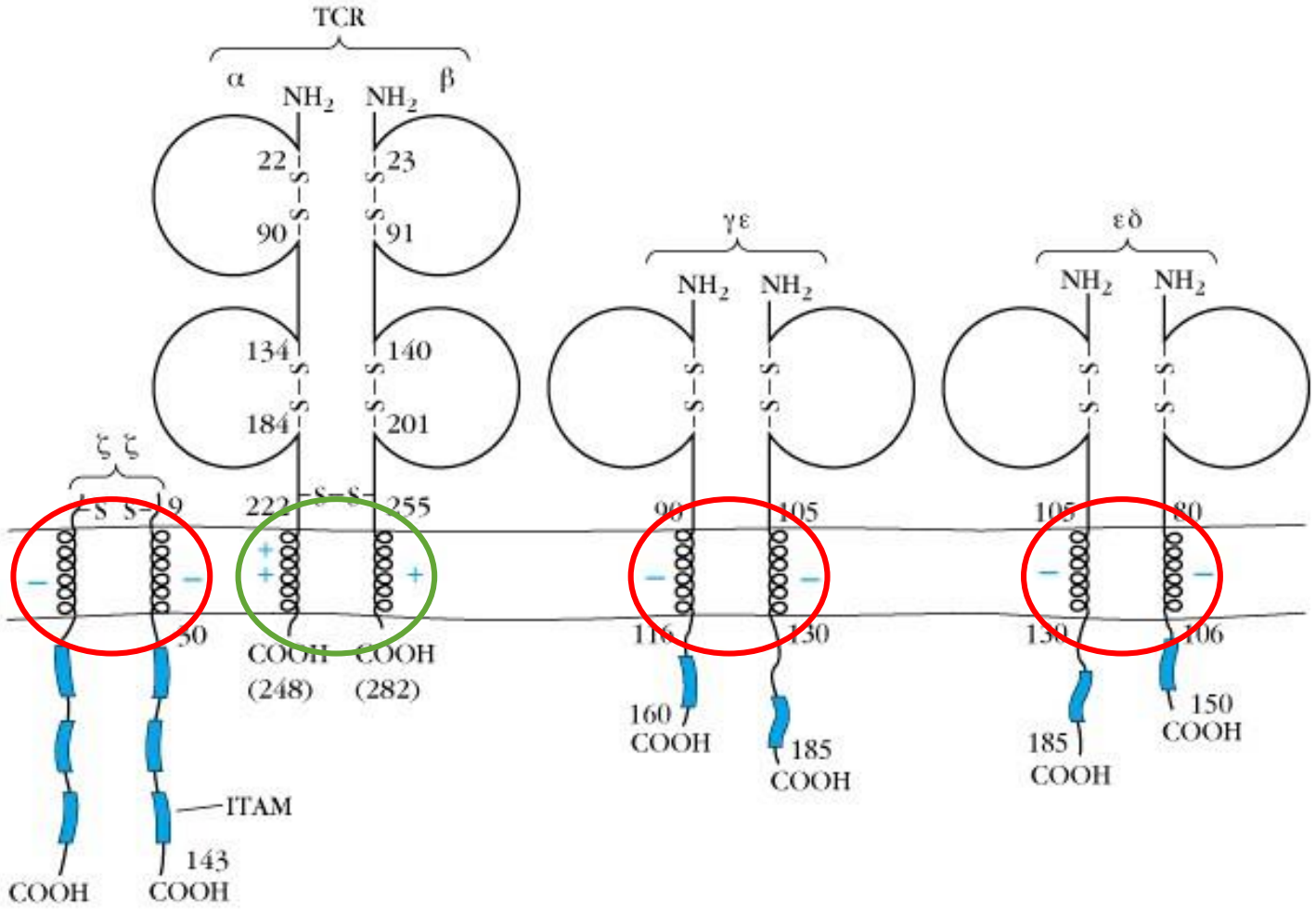




Las cadenas CD3 y ζ son constantes en todos los LT.

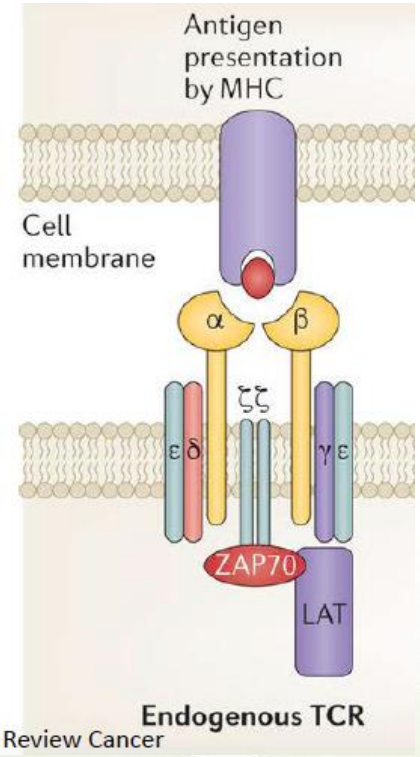
Complejo CD3-TCR:asociación de elementos

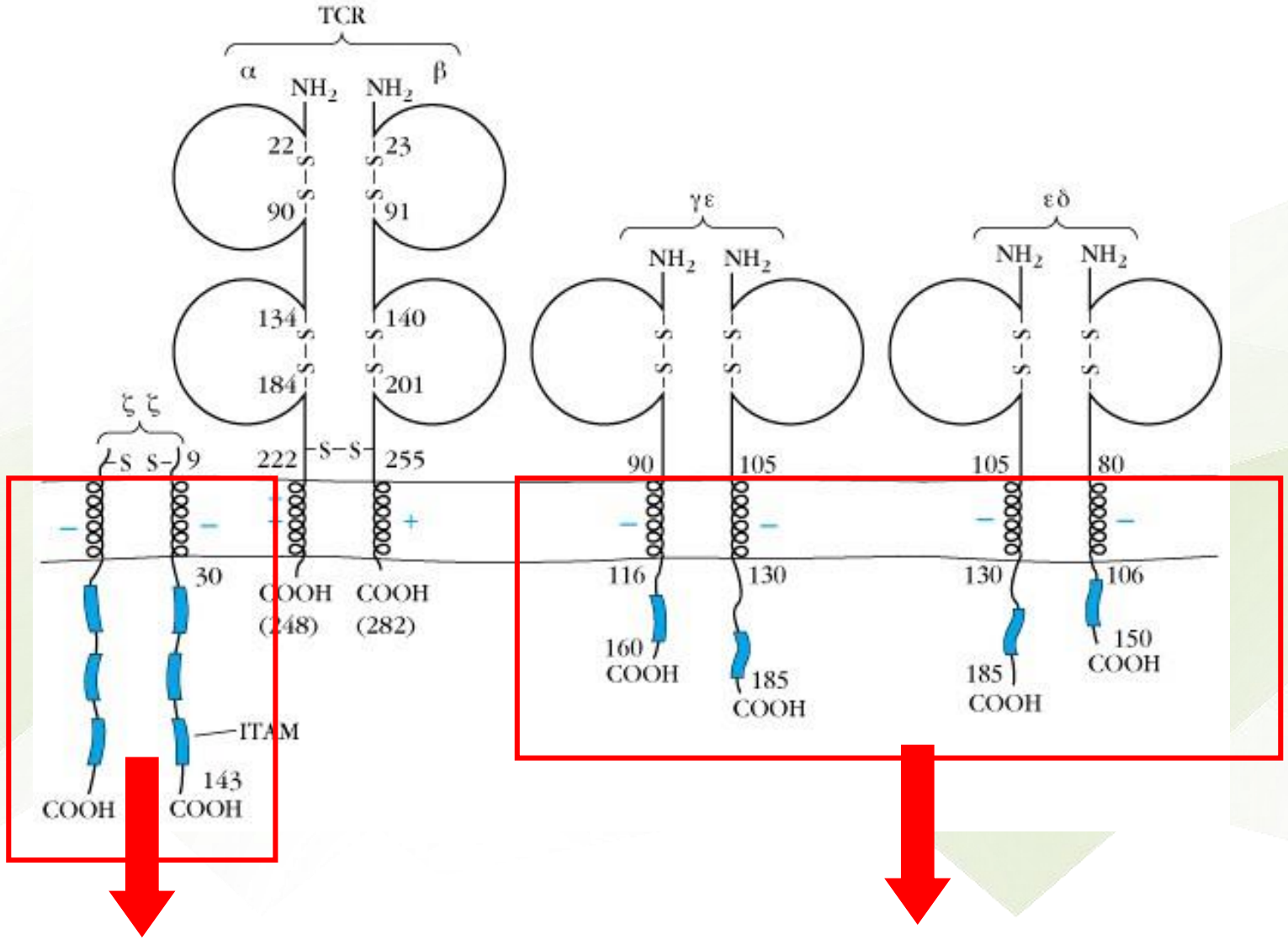




Cargas negativas de Asp en CD3 y ζ interactúan con cargas positivas del TCR

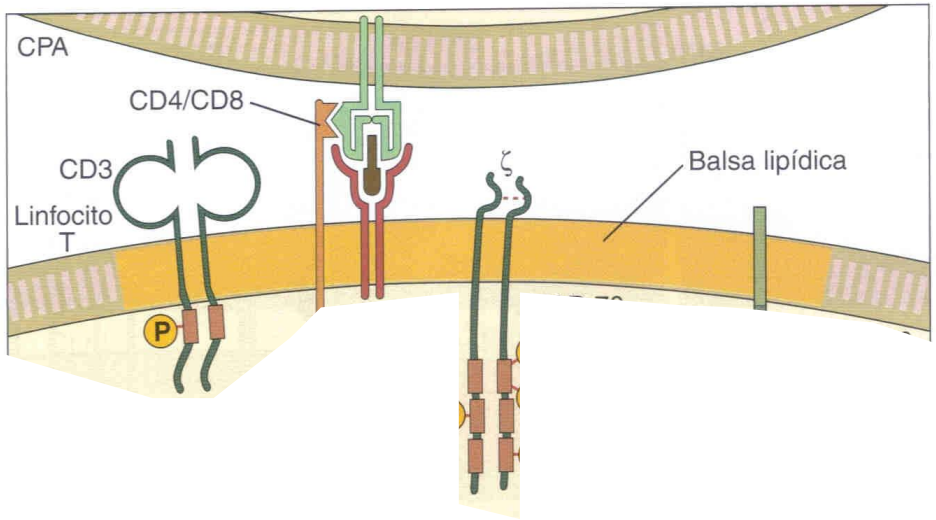
Complejo CD3-TCR: transducción de señales





CD3 y ζ no son responsables del reconocimiento de Ag sino de transducción de señales: motivos ITAM

Vías de señalización en la activación de LT

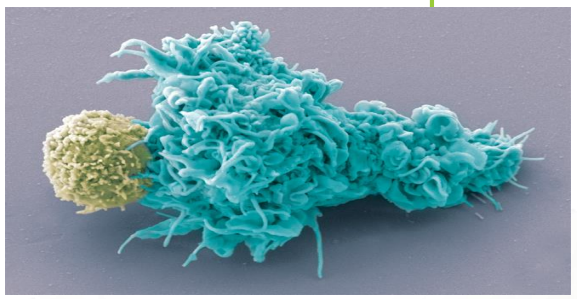


Cinética

1. Entrecruzamiento de múltiples receptores. Cambios conformacionales

Expresión de genes (citoquinas, moléculas inflamatorias, efectores…)

SEÑALIZACIÓN DEL RECEPTOR T EN LA SINAPSIS INMUNOLÓGICA



Outer ring (red) pSMAC	Inner circle (green) cSMAC
LFA-1:ICAM-1	TCR, CD4, CD28 MHC:peptide

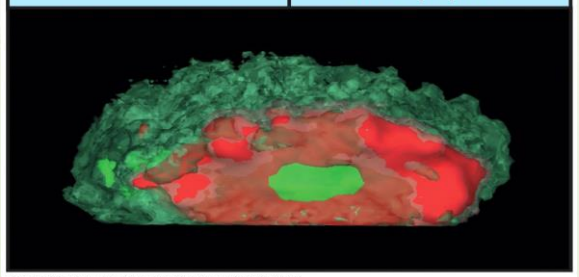
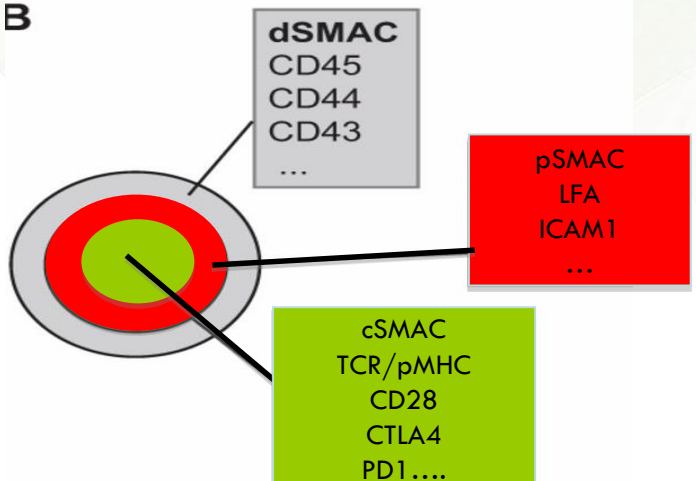
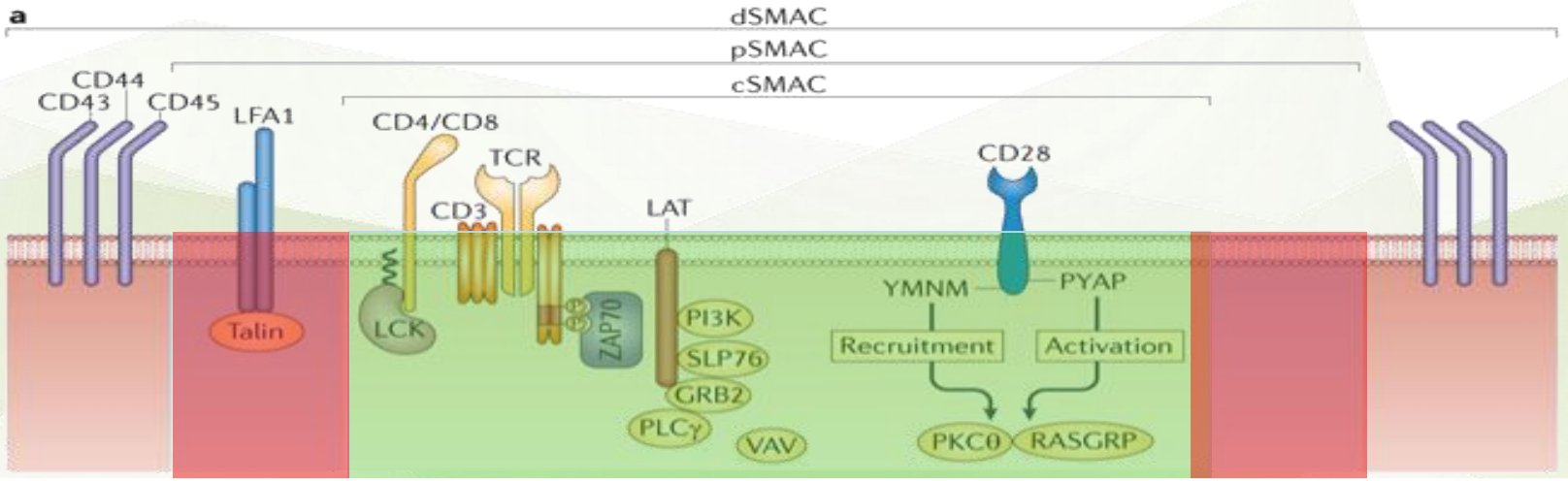


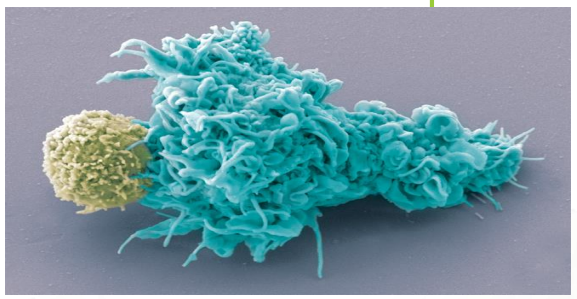
Figure 8-30 Immunobiology, 6/e. (© Garland Science 2005)





Chen and Flies, Nature Reviews Immunology

MOLÉCULAS CO-ESTIMULADORAS Y CO-INHIBIDORAS DE LOS LINFOCITOS T



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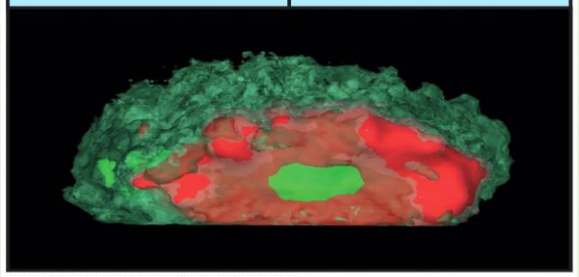

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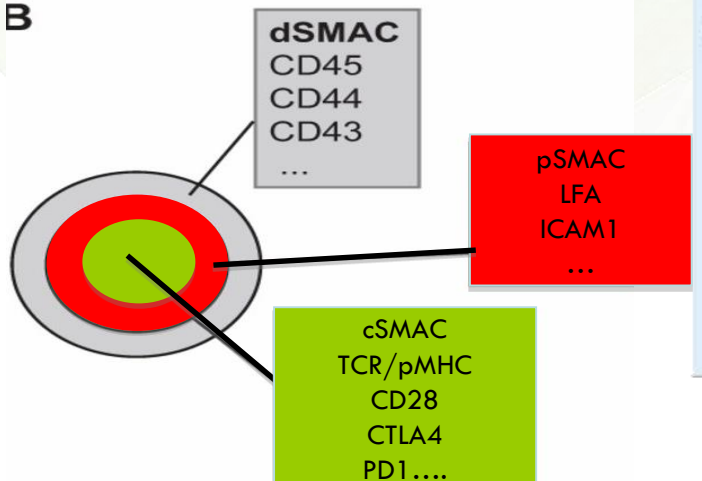
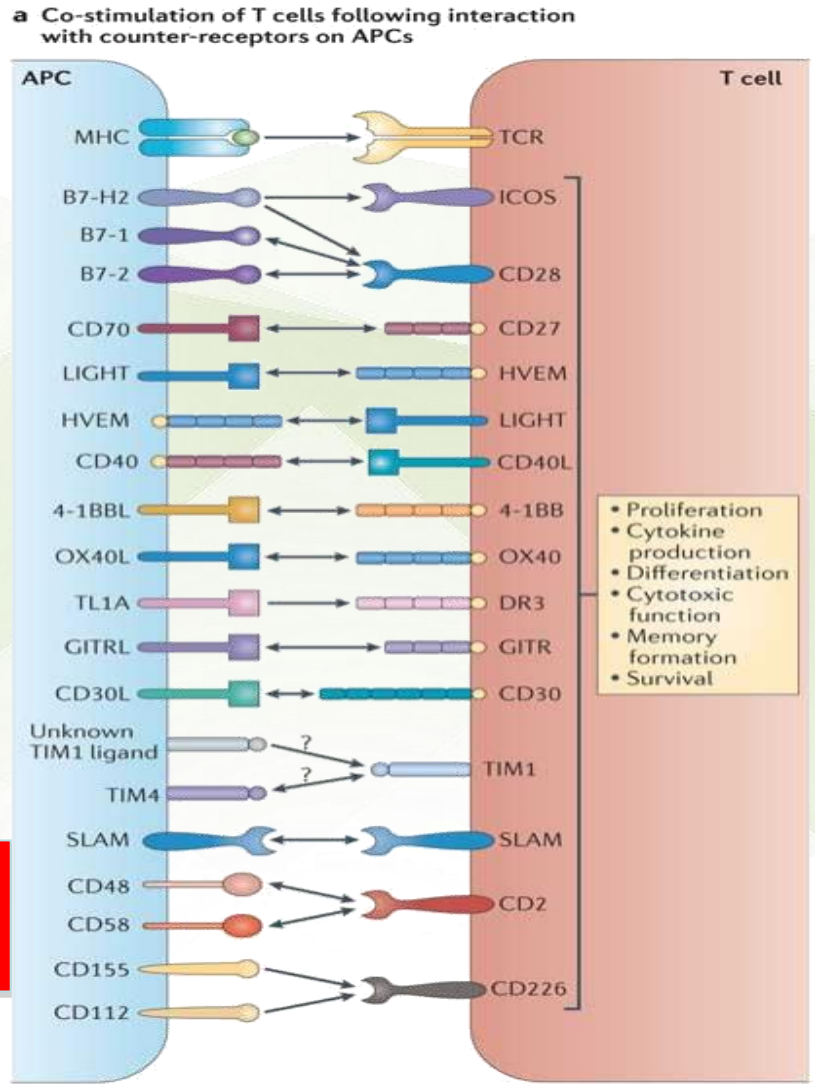
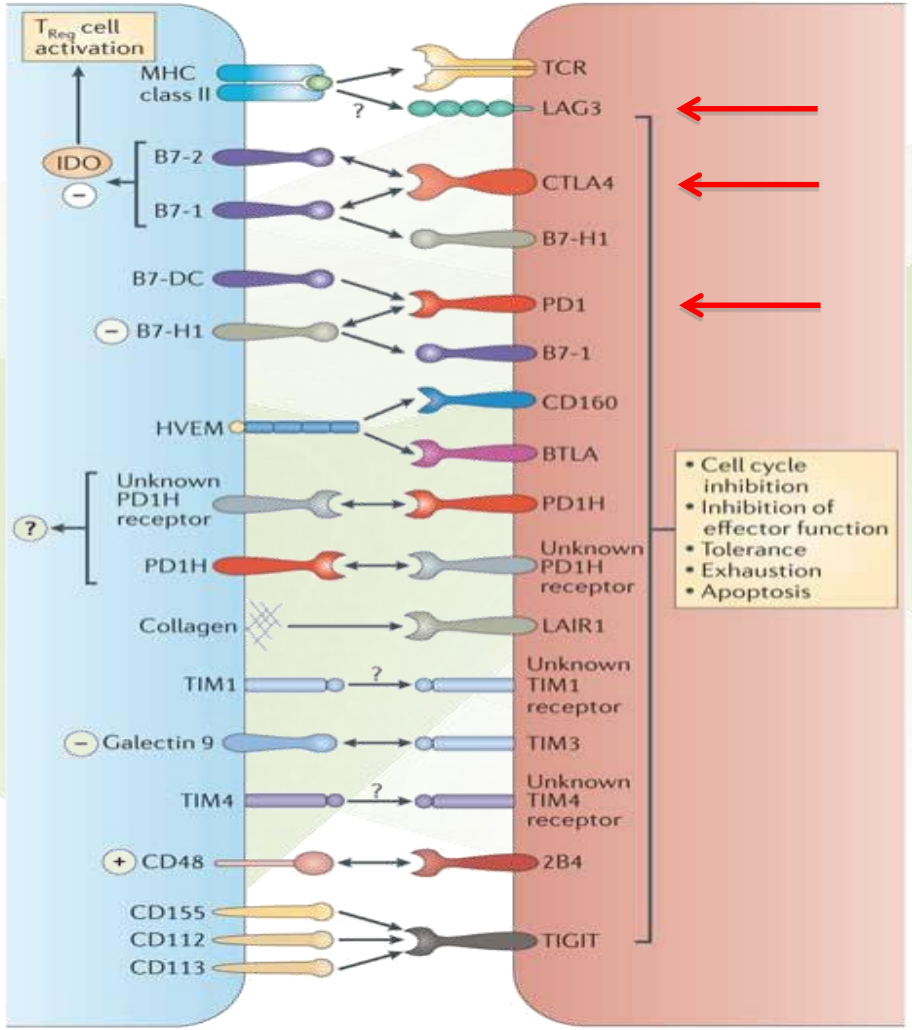
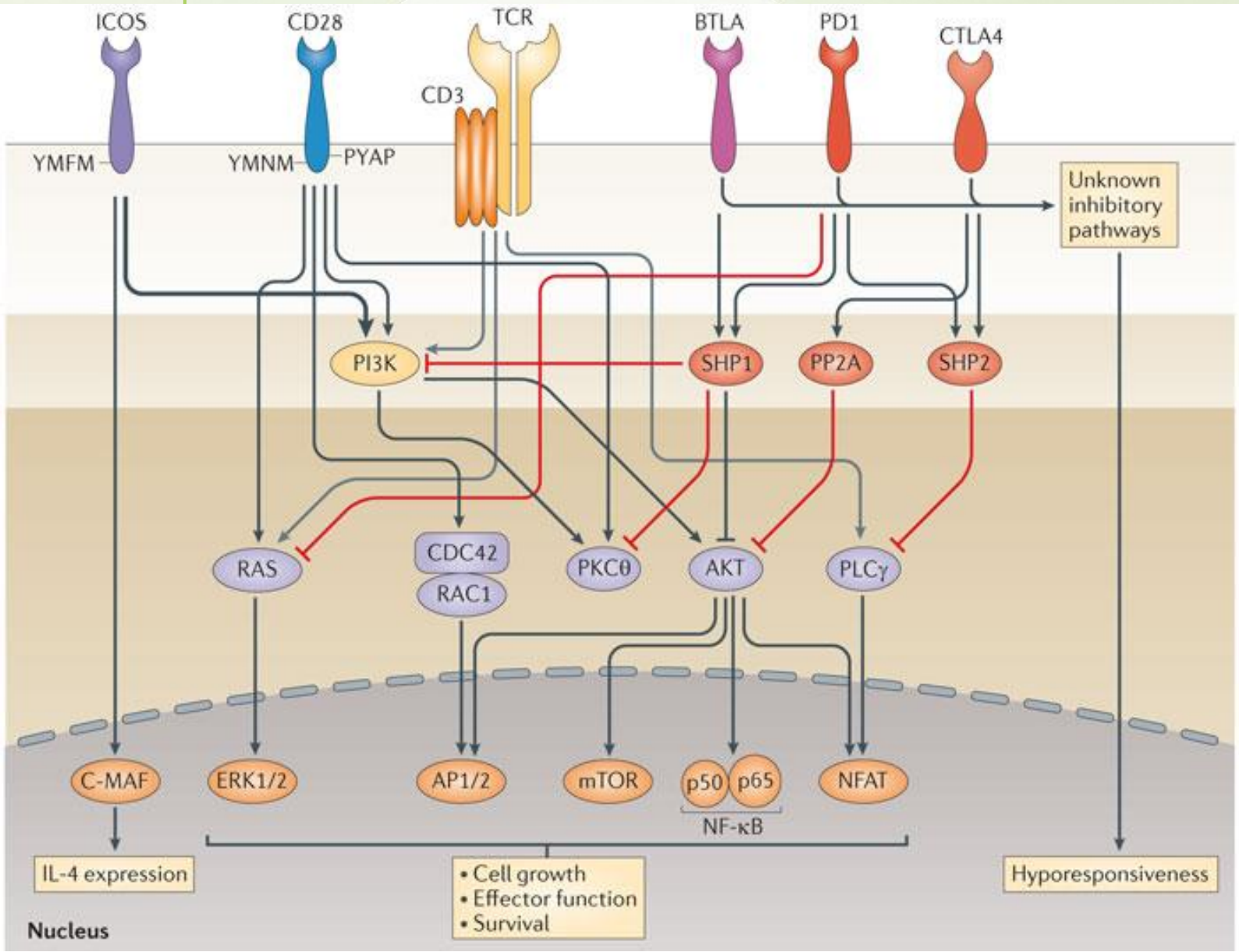






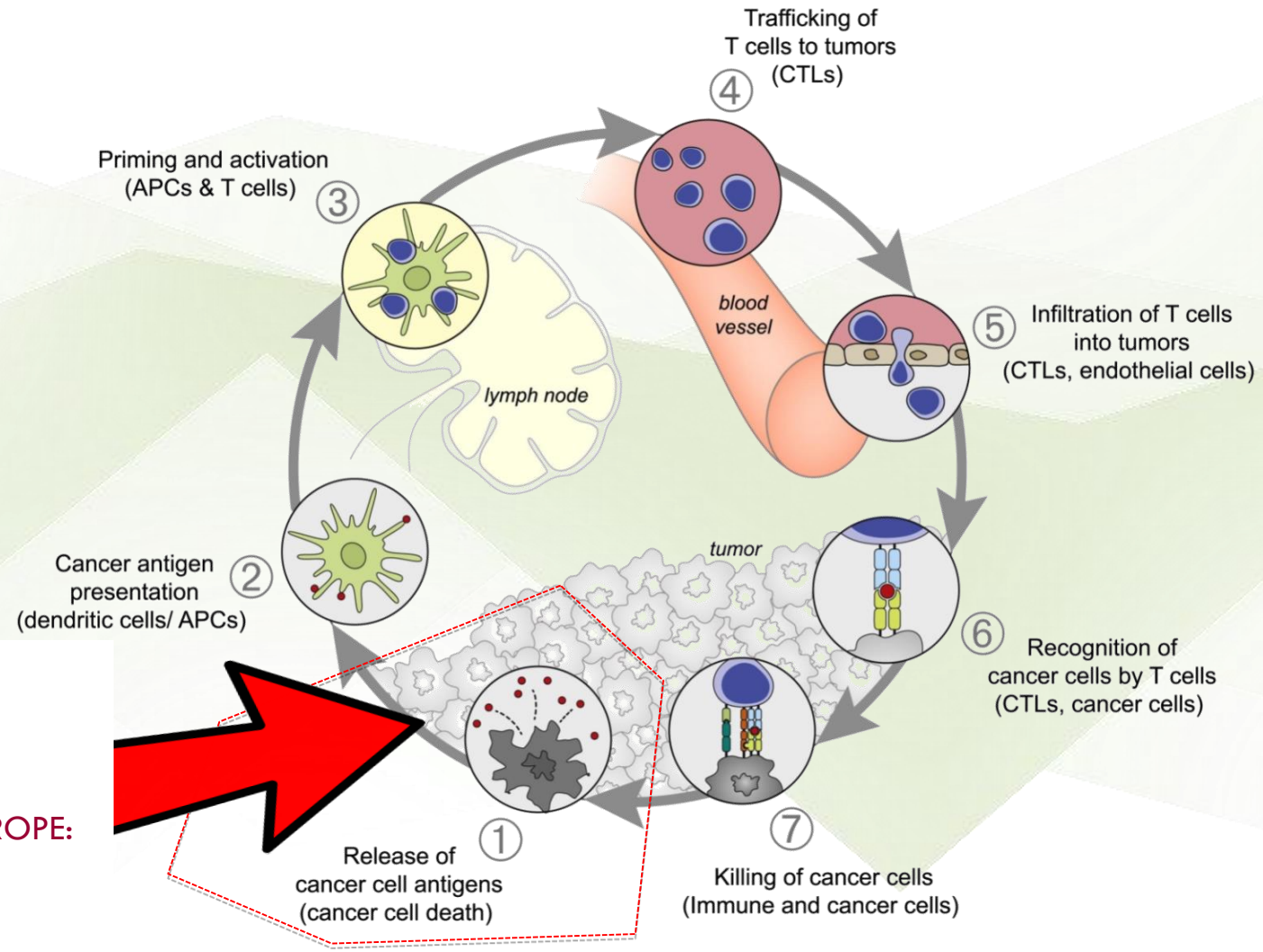
Chen and Flies, Nature Reviews Immunology

Vías de señalización coestimuladoras y coinhibidoras "downstream" de los receptores de la familia CD28.



Chen anf Flies, Nat Rev Immunol 2013

Mecanismos de evasión tumoral
El ciclo "inmunidad-cancer"



- APOPTOSIS:
- NECROSIS:
- AUTOPHAGY:
- MITOTIC CATASTROPE:
- SENESCENCE

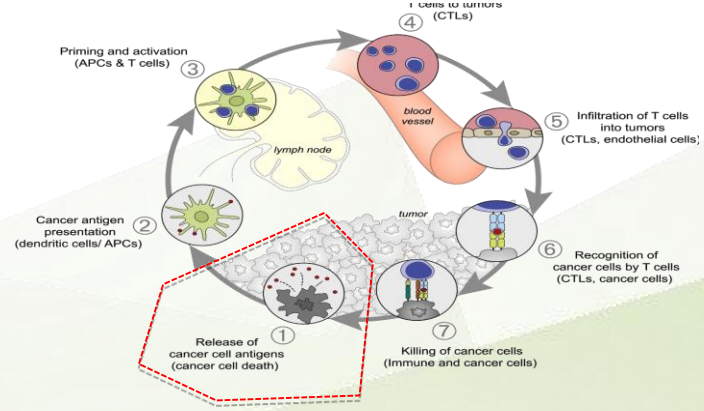
Immunogenic cell death

Chen and Mellman. Immunity. 2013

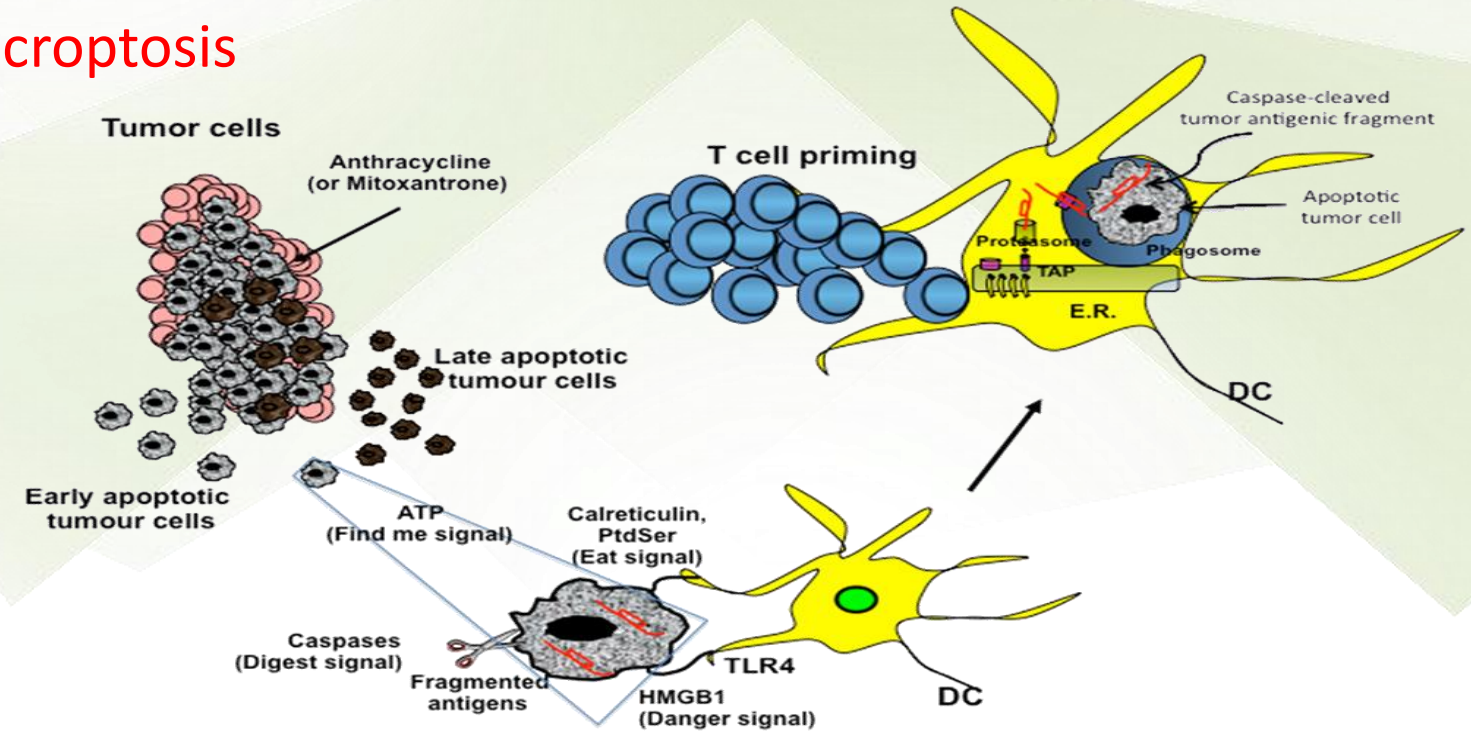
1. Liberación de antígenos por la célula tumoral: Muerte celular inmunogénica (ICD)

Requisitos moleculares para inducir una muerte inmunogénica:

Secreción de ATP ("find me" signal)
Exposición de calreticulina en la membrana ("eat me" signal)
Secreción de HMGB1



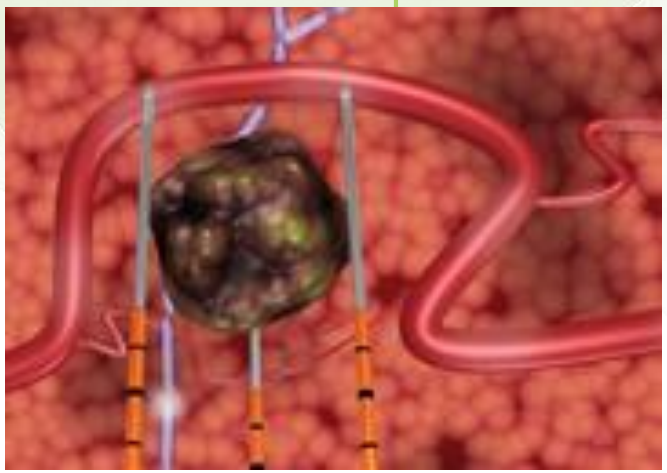
Necroptosis



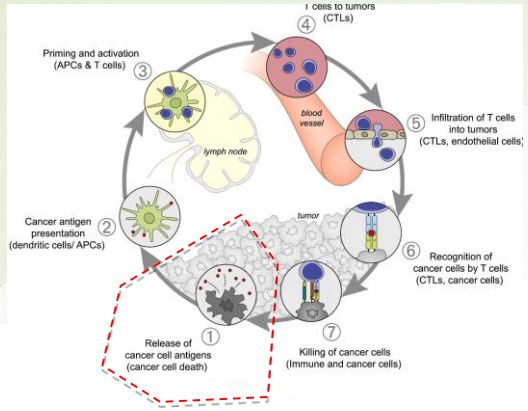
Bortezomib, Doxorubicina, epirubicina, mitoxantrone, Oxalipatino…

Zitvogel et al 2013

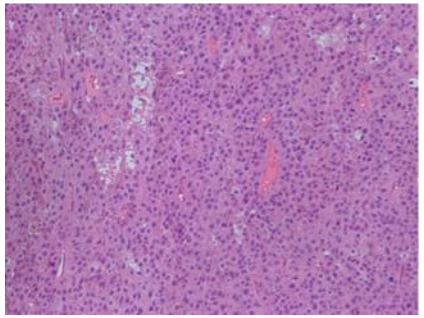
Inducción de muerte celular inmunogénica Irreversible electroporation (IRE).



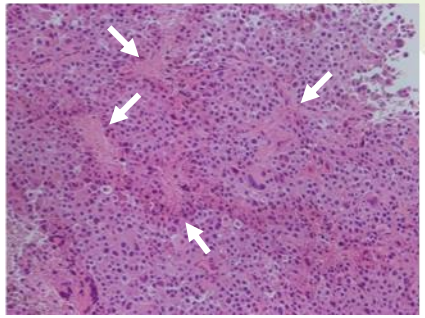
IRE: campos eléctricos ultracortos pero fuertes para crear nanoporos permanentes y letales en la membrana celular.
Muerte inducida por apoptosis



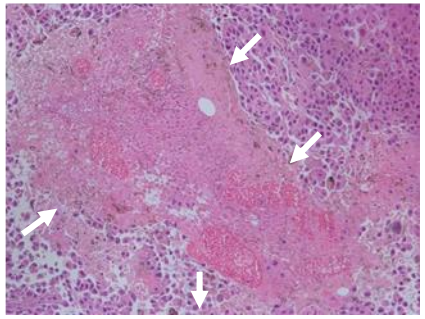
A Control



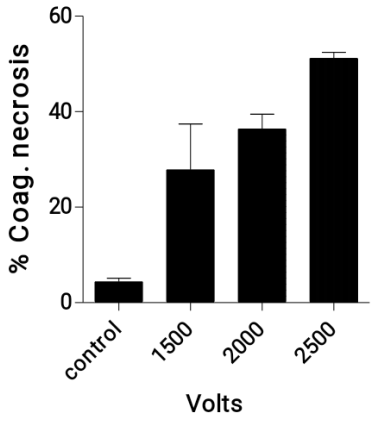
B IRE 2000v



C IRE 2500v



D



Poly ICLC: dsRNA

Tumor 5mm

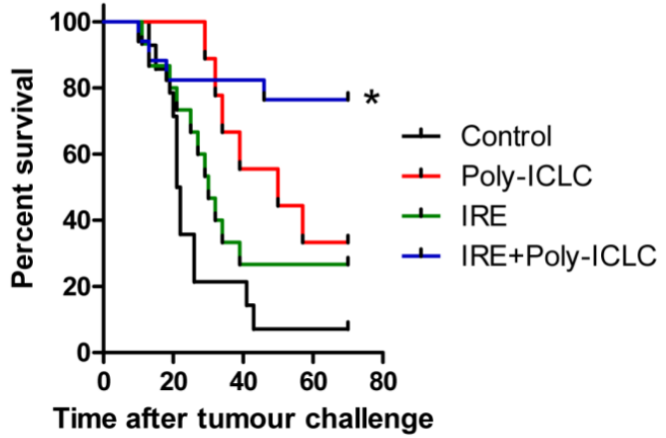
IRE + Poly ICLC

10

C3H

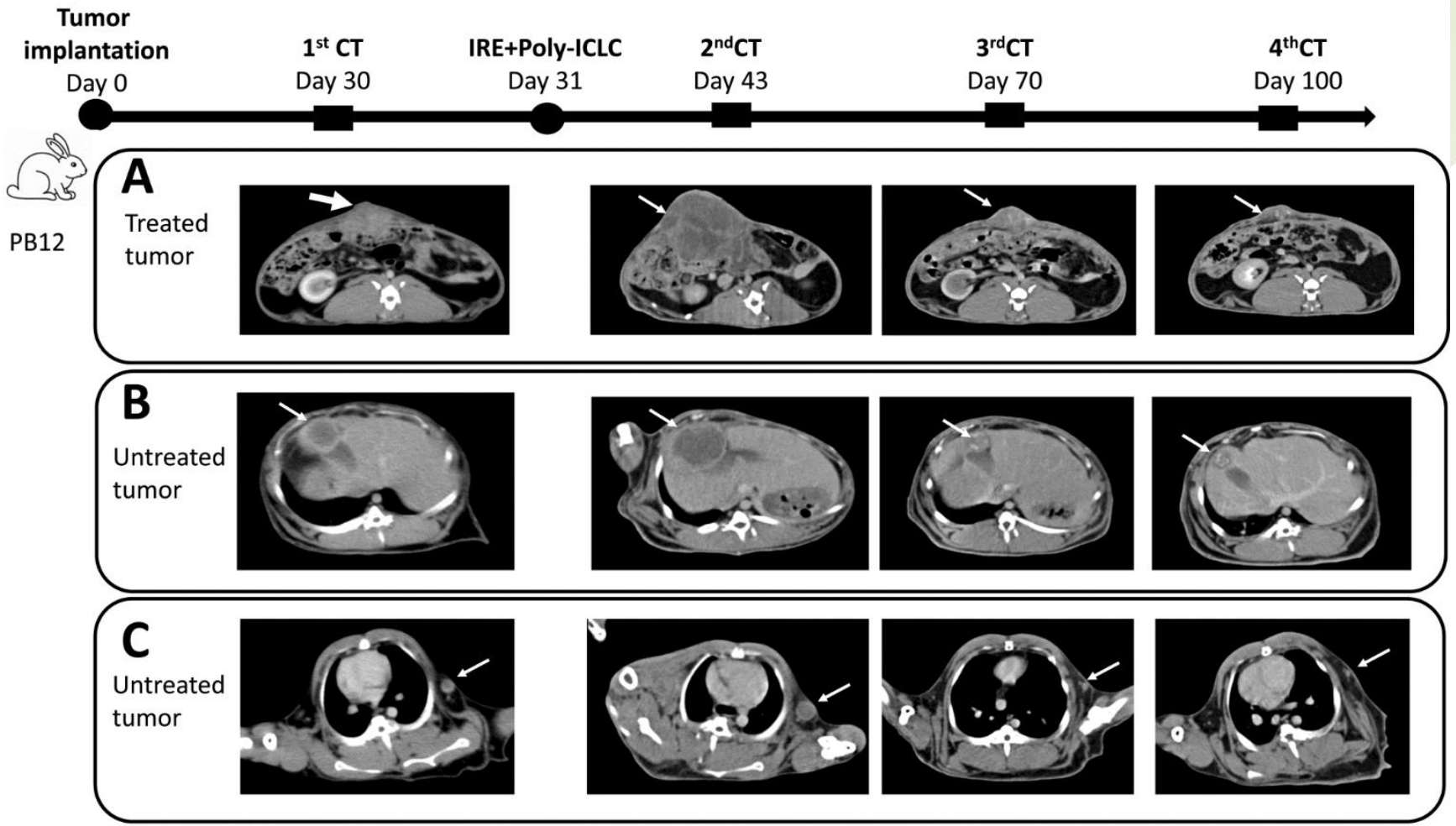
Hepa.129

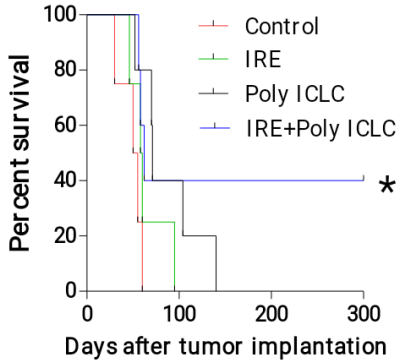
Tumor follow up



Vivas et al, JVIR, 2019

Therapeutic effect of IRE + Poly-ICLC in rabbits: Abscopal effect.

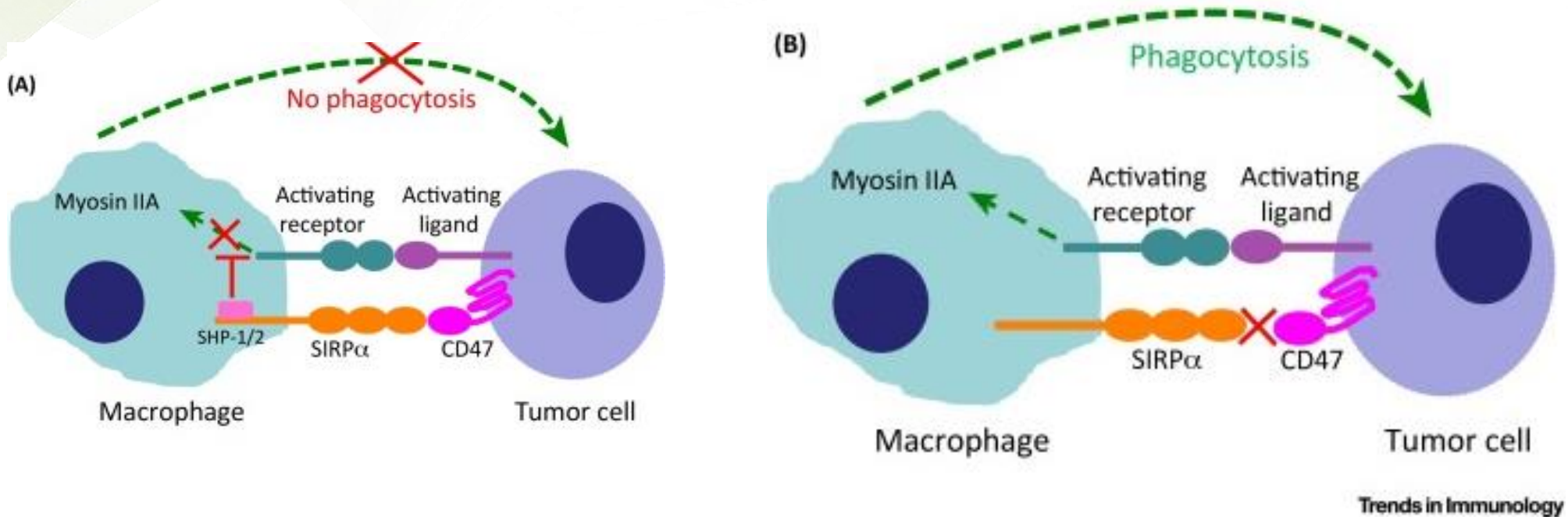




In situ vaccination

Vivas et al, 2019,

Estrategias de escape a la presentación antigénica
CD47: “a don´t eat me signal”

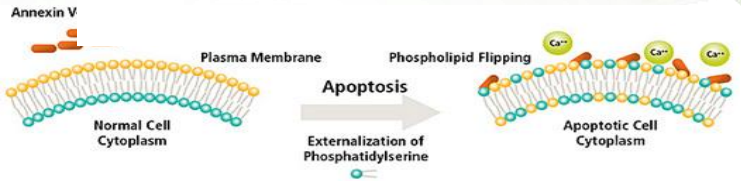


Veillette and Chen, Trends Immunol 2018

Fosfatidilserina: inhibidor de la respuesta inflamatoria
Tras la muerte celular

Fostatidilserina (PS):

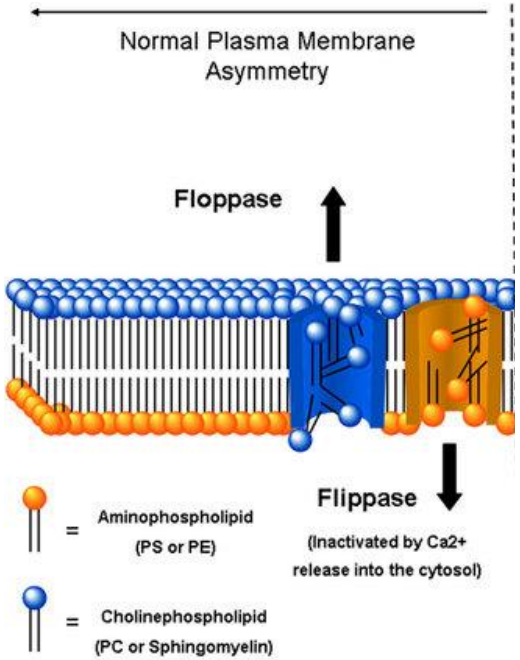
- Fosfolípido cara interna membrana celular
- Apoptosis → Monocapa celular exterior
- Señal "eat me" para fagocitos
- Función **inmunosupresora**



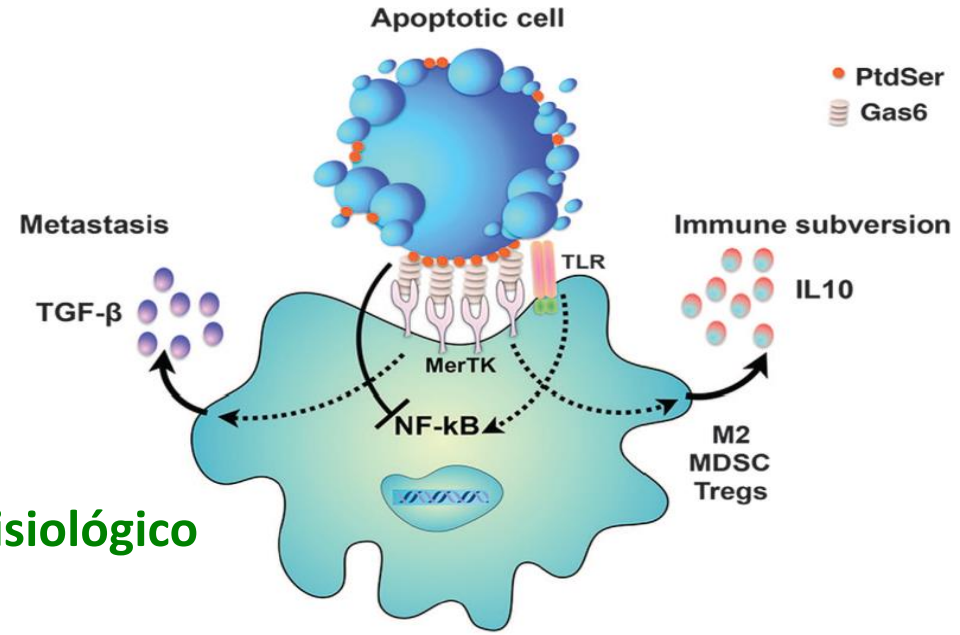
Receptores TAM:

- Tyro3, Axl, and Mer
- Macrófagos, DCs, MDSCs (Células mieloides supresoras), NK, plaquetas, mastocitos y fibroblastos asociados a cáncer (CAFs).
- Ligandos: Proteína S, Gas6
- Función:

Inhibir la respuesta inflamatoria innata



Mecanismo fisiológico

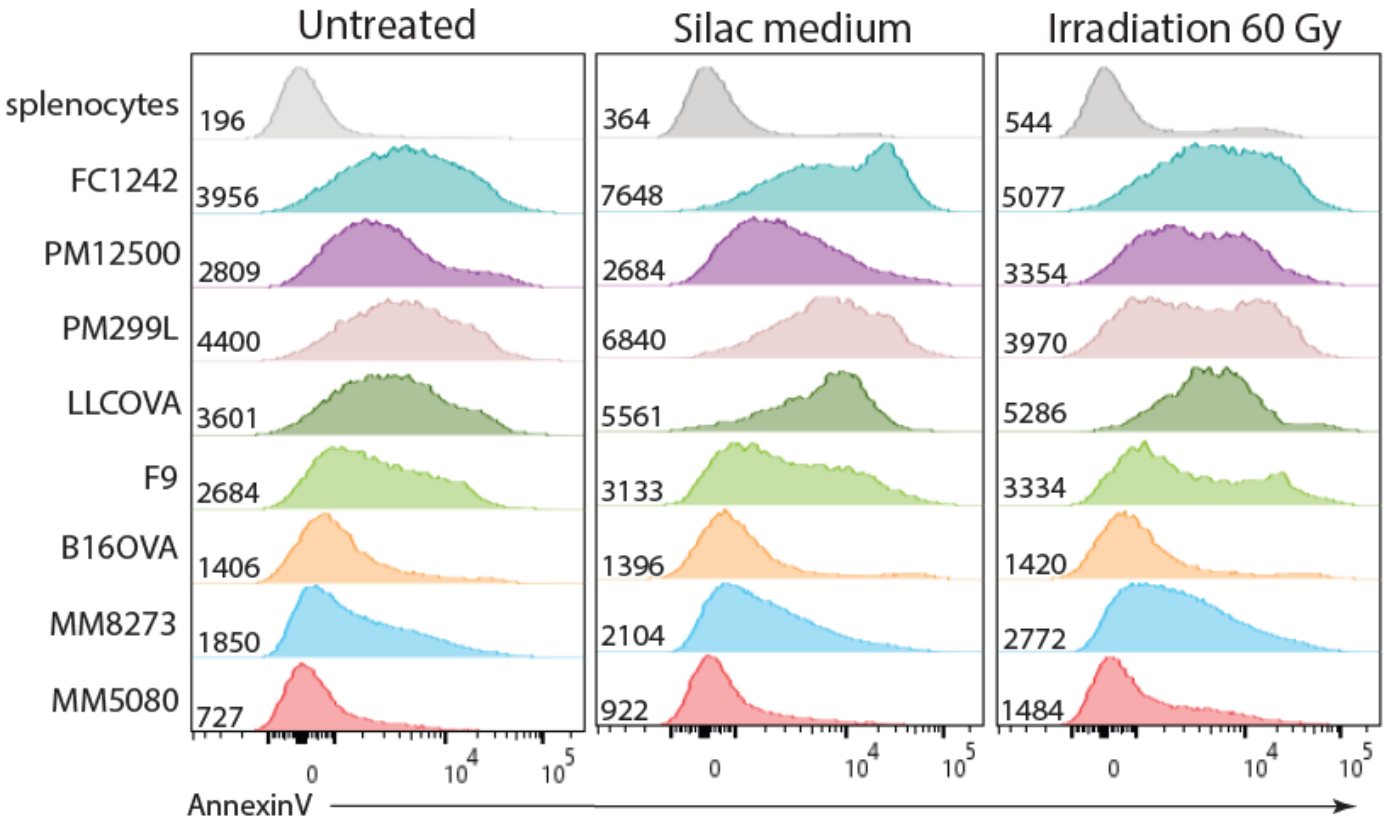


Birge et al, 2016

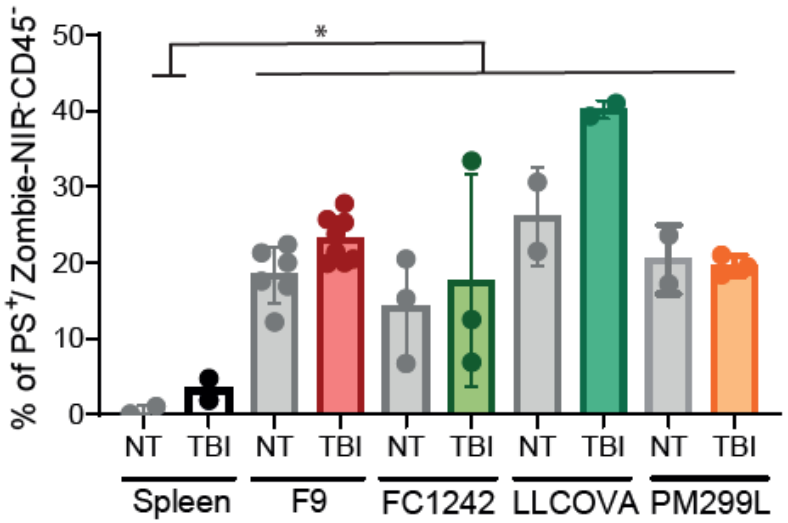
Immune escape response

PS se expone en líneas celulares tumorales y se une a la anexina V

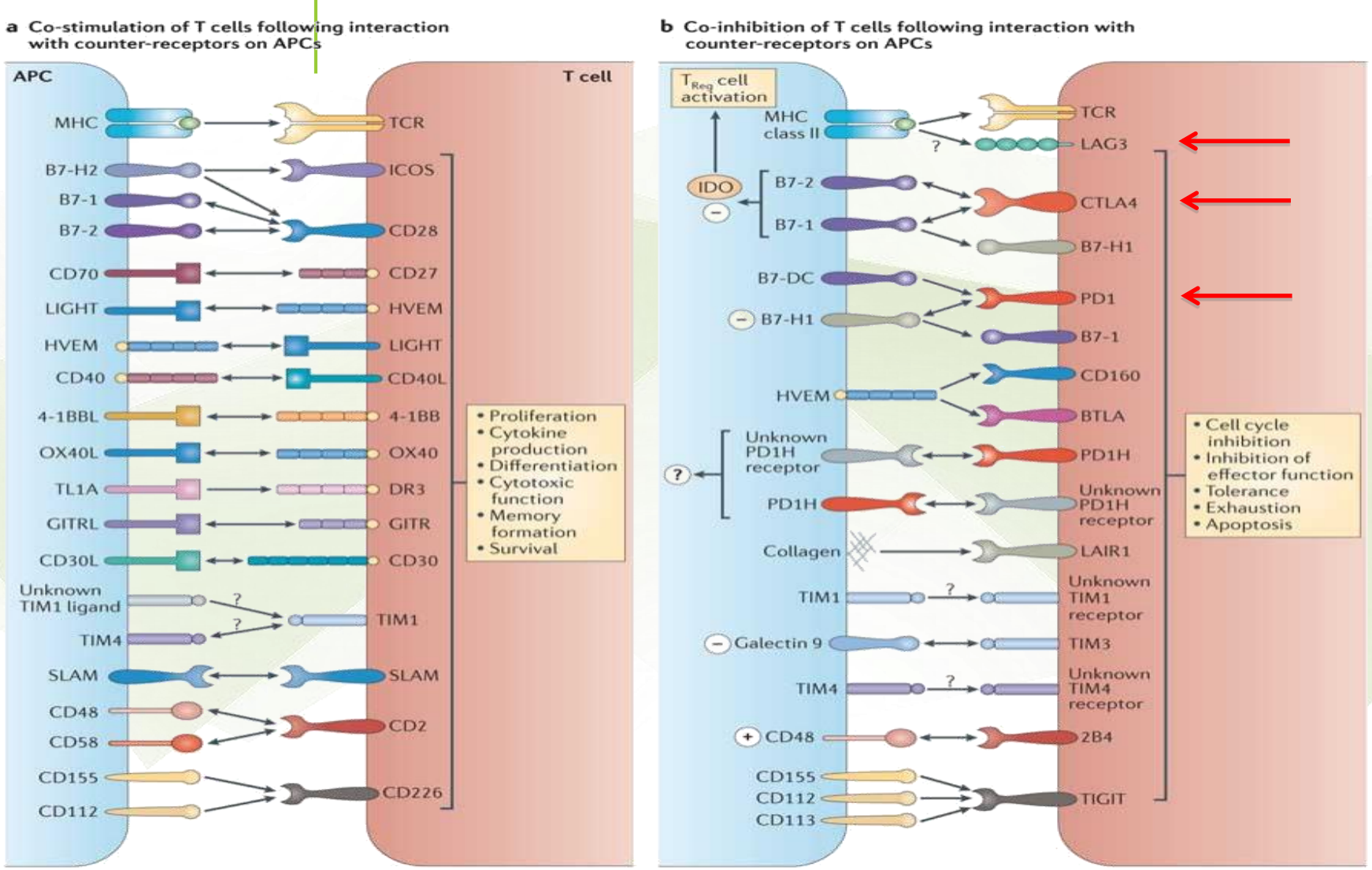
Expresión PS
en líneas celulares tumorales murinos

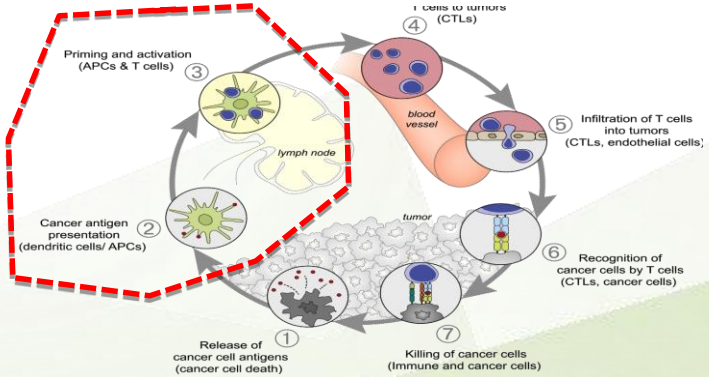


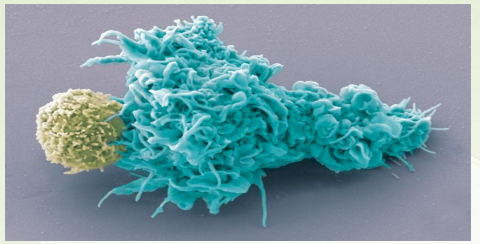
Expresión PS
en tejidos tumorales murinos



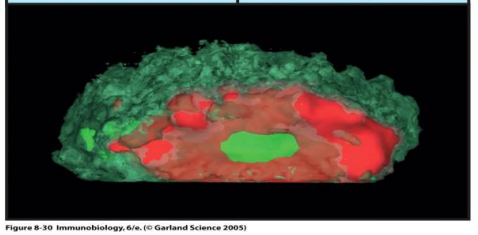
2 Y 3. PRESENTACIÓN ANTIGÉNICA Y ACTIVACIÓN DE LA RESPUESTA INMUNE







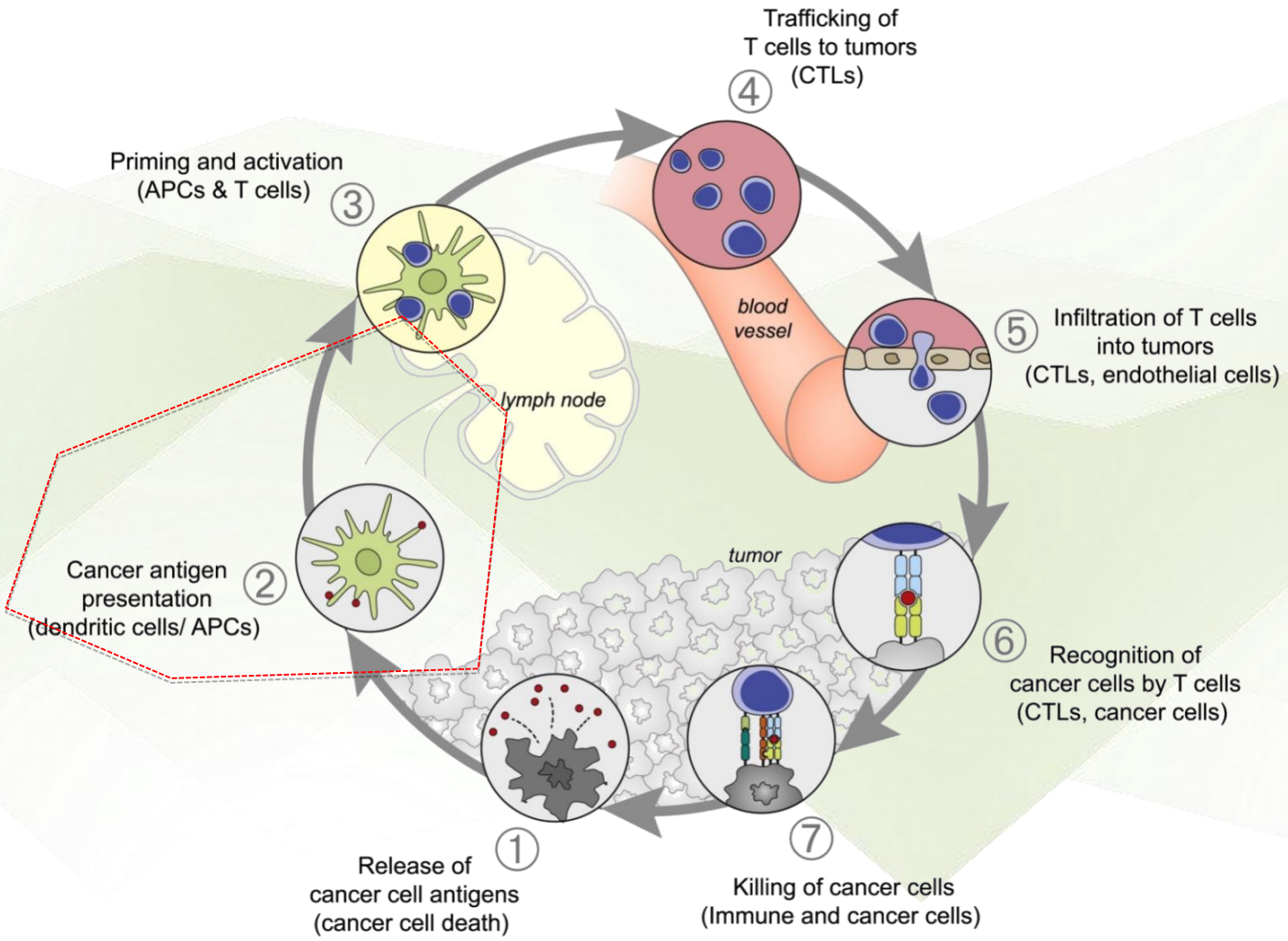
Outer ring (red) pSMAC	Inner circle (green) cSMAC
LFA-1:ICAM-1	TCR, CD4, CD28 MHC:peptide



Chen and Flies, Nature Reviews Immunology

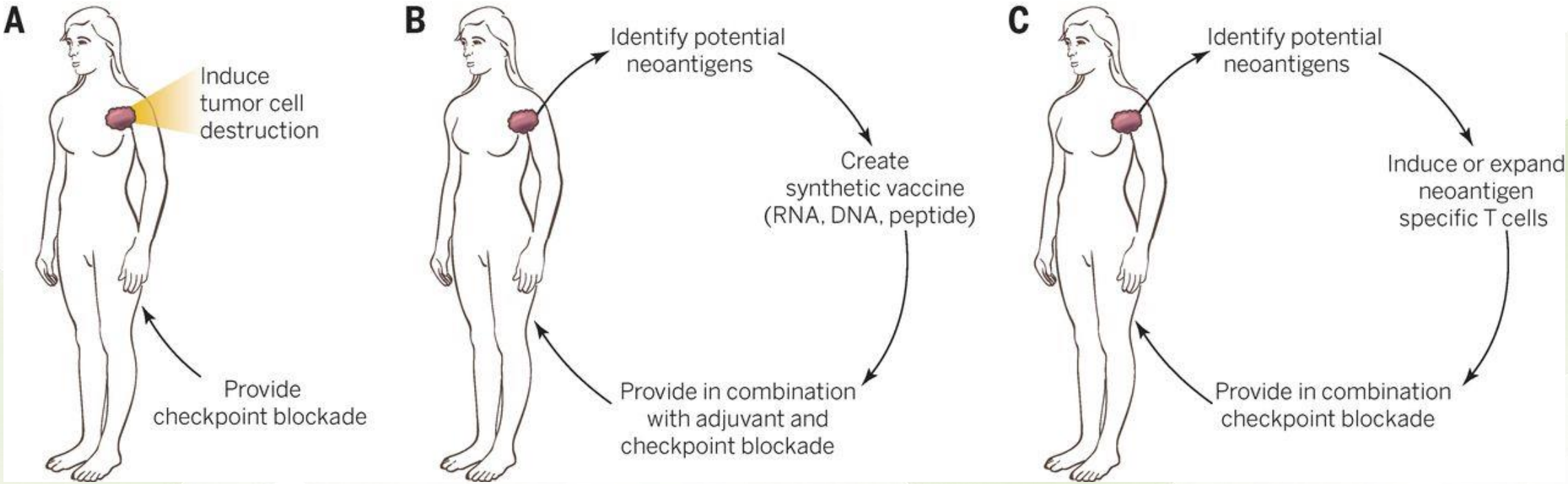
Mecanismos de evasión tumoral
El ciclo "inmunidad-cancer"

Vacunación



Chen and Mellman. Immunity. 2013

Estrategias para dirigir la respuesta inmune frente al repertorio NeoAgs específico del paciente



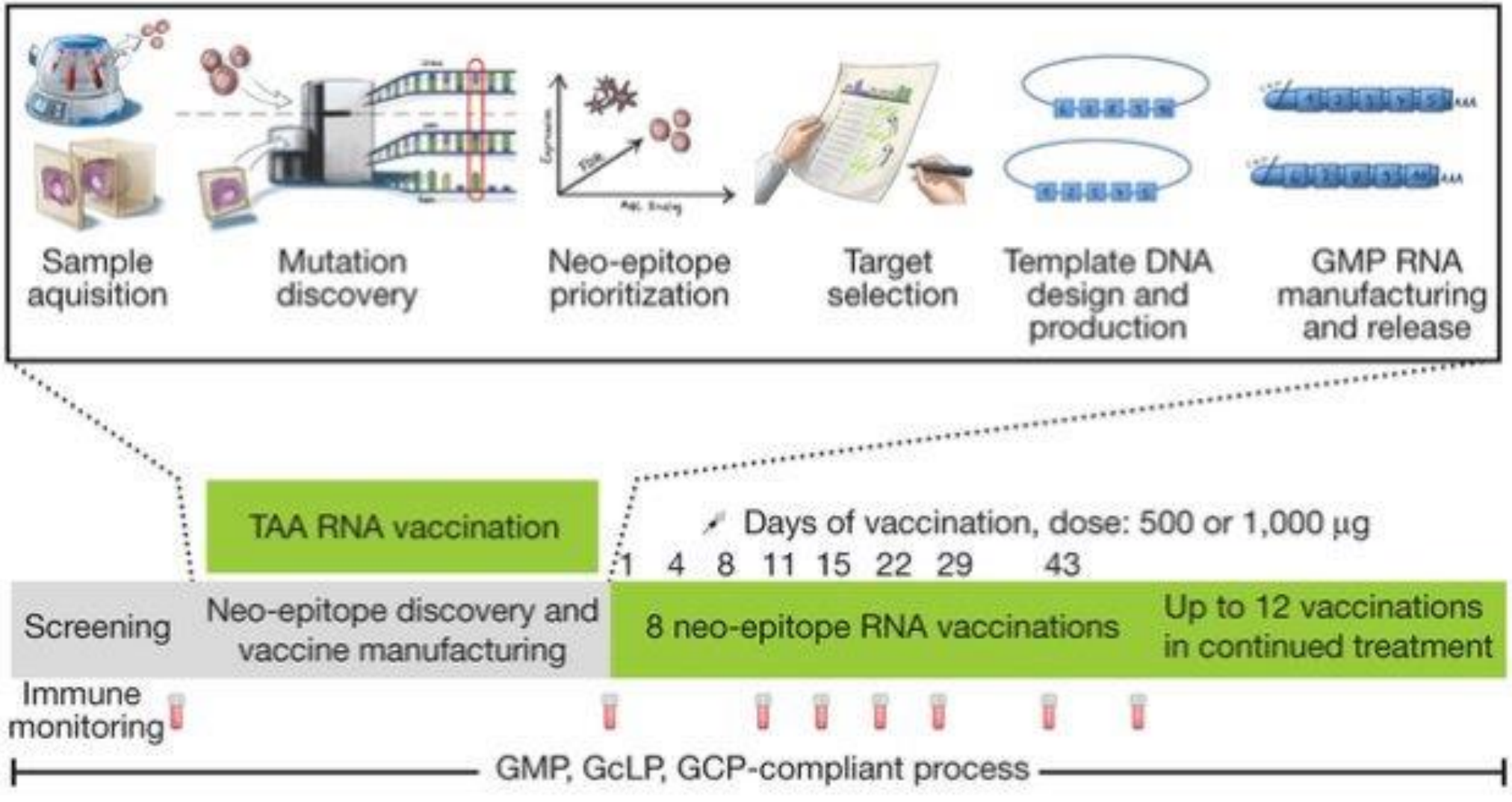
Radioterapia
Virus oncolíticos

Ton N. Schumacher and Robert D. Schreiber. Science, 2015

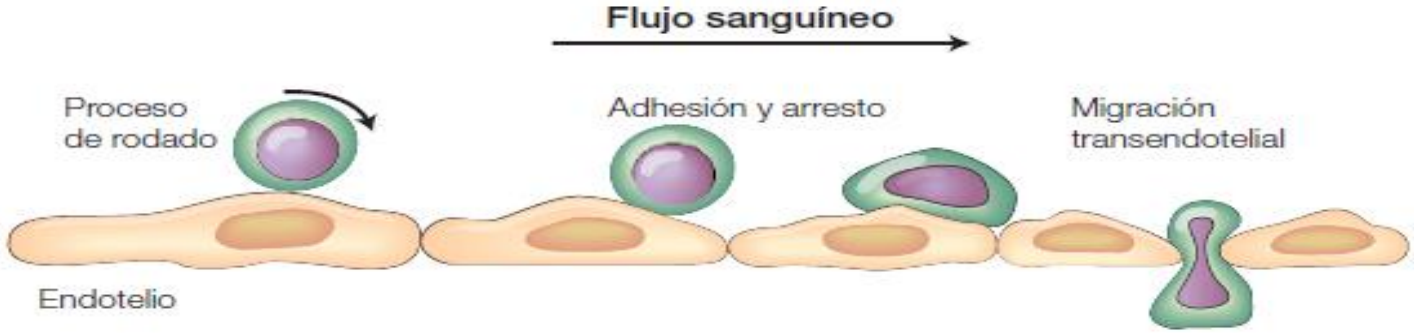
Vacunas personalizadas basadas en neoantígenos : un nuevo enfoque para la inmunoterapia contra el cáncer

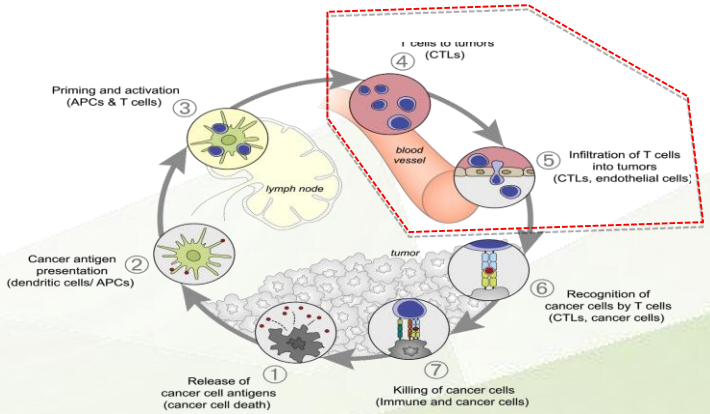
Bioorg Med Chem. 2017 Oct 19. pii: S0968-0896(17)31220-8.

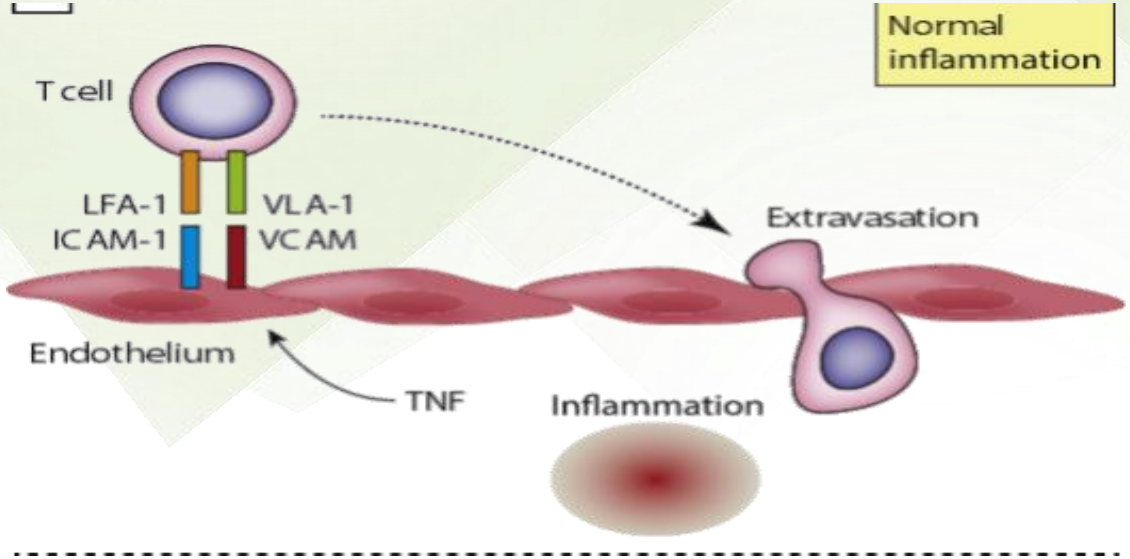
Personalized #CancerVaccine
personal RNA “Mutanome” to prime PolySpecific Immunity
UgurSahin #BioNTech
@nature http://buff.ly/2sMOdYm

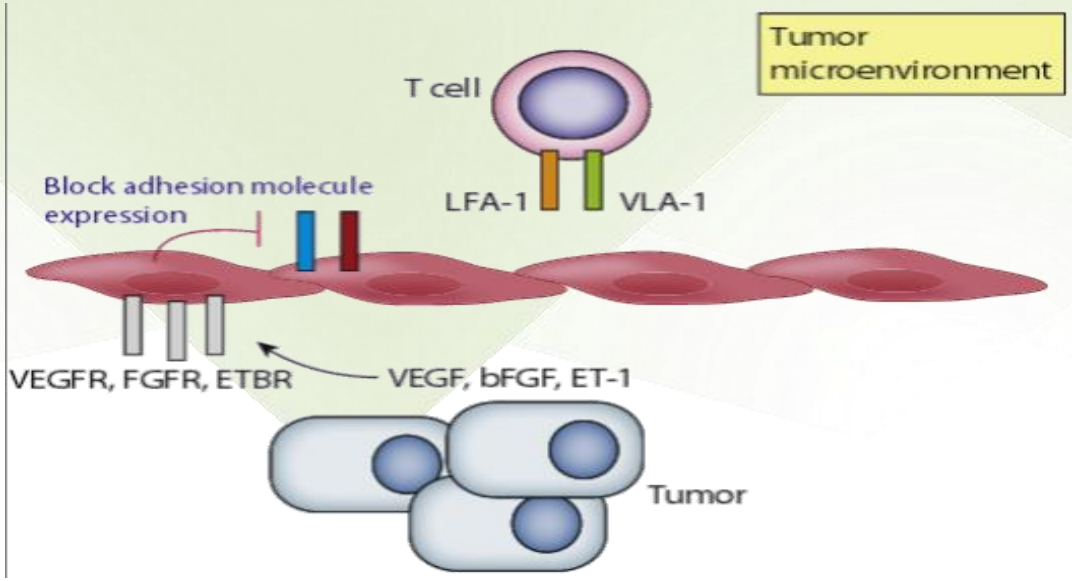


4 Y 5. EL ENDOTELIO: UNA BARRERA FÍSICA PARA EL TRÁFICO DE CÉLULAS T



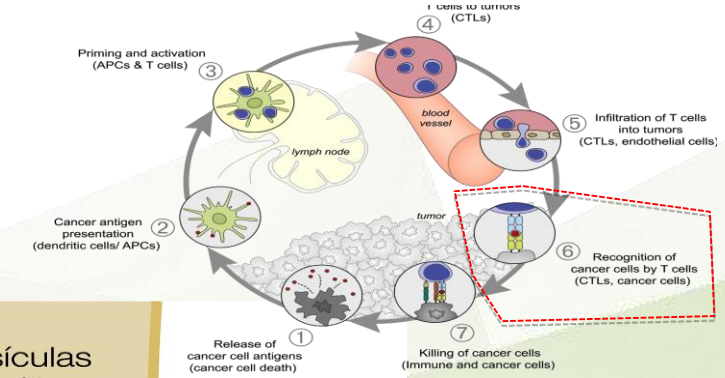


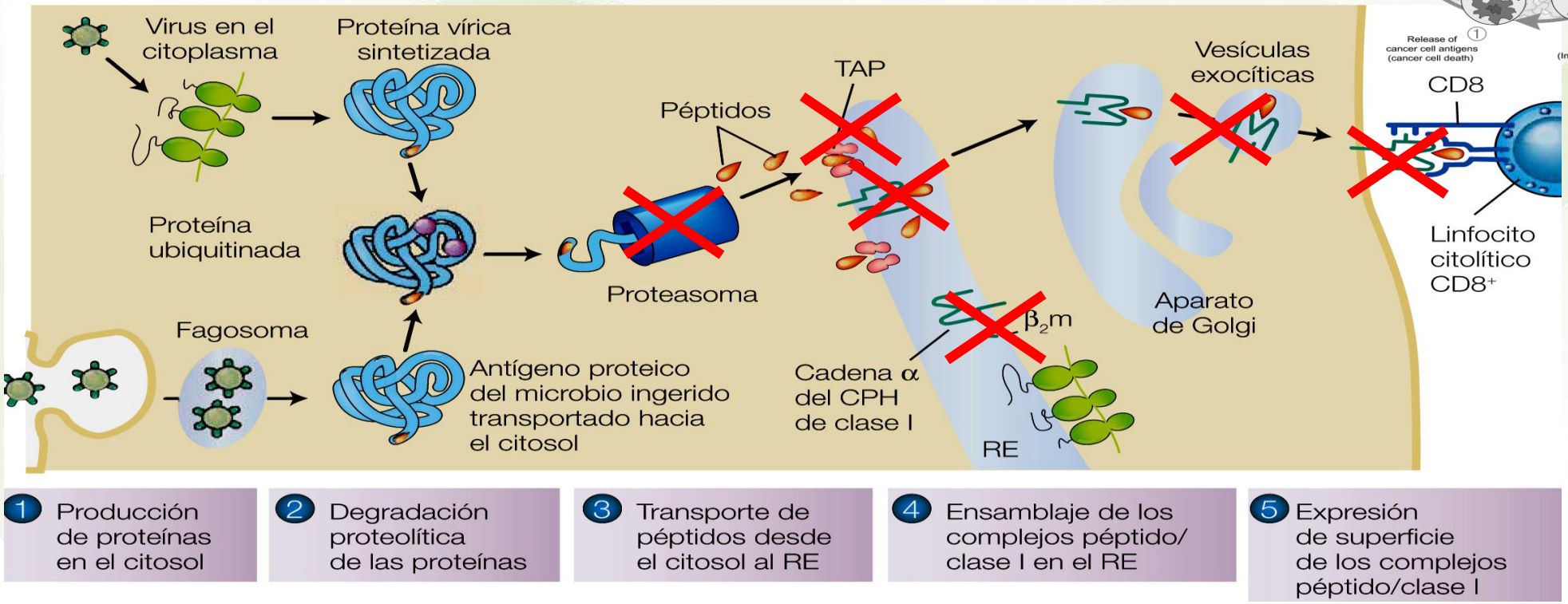




6. PRESENTACIÓN ANTIGÉNICA: RECONOCIMIENTO DEL AG EN EL TUMOR.

Problemas que aparecen en la maquinaria de presentación de antígenos en el cáncer



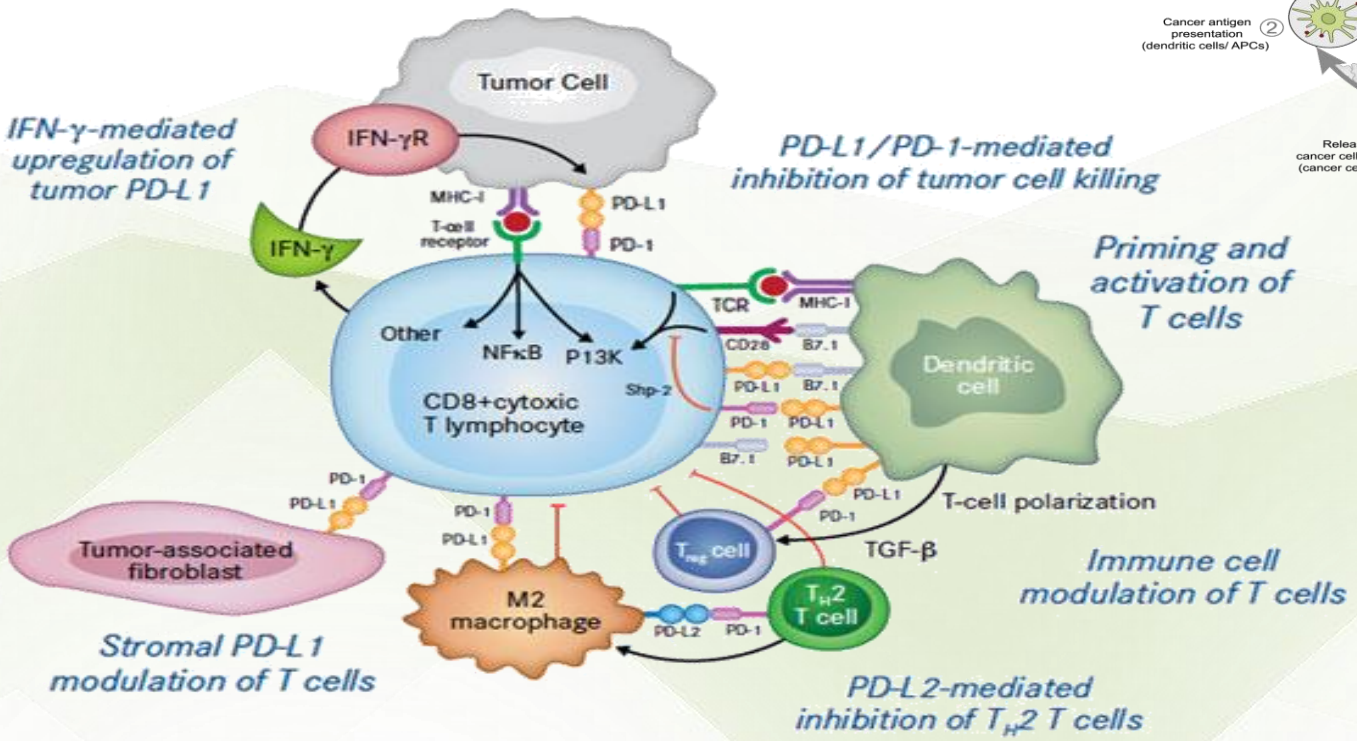


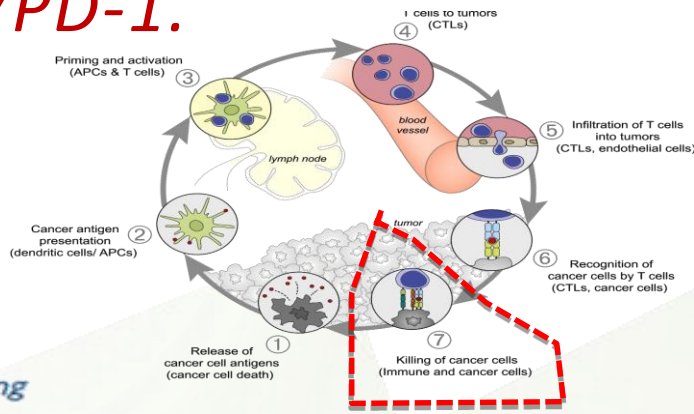
•Carcinoma colorectal, vejiga, ovario meduloblastoma, leucemia mieloide aguda carcinoma de cabeza y cuello, esófago, estómago, cervix, astrocitoma, próstata, melanoma…

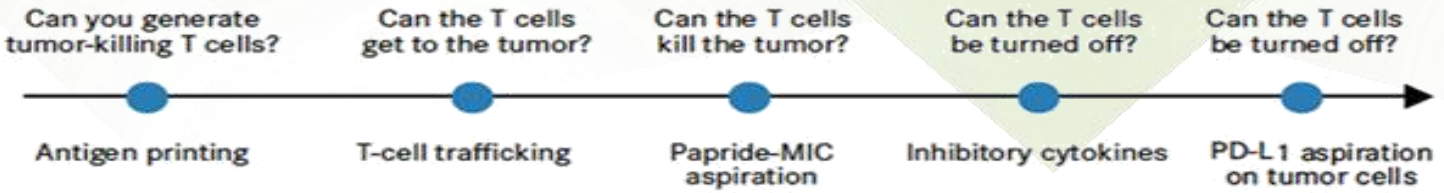
Revisado en Leone P et al. JNCI J Natl Cancer Inst 2013;105:1172-1187

LA SINAPSIS INMUNOLÓGICA CITOTÓXICA INMUNOLOGÍA TUMORAL Y LA VÍA PD-L1/PD-1.

Cancer Type	% With Positive PD-L1 Expression
Melanoma	40-100
Non-small cell lung cancer	35-95
Nasopharyngeal	68-100
Glioblastoma/mixed glioma	100
Colon adenocarcinoma	53
Hepatocellular carcinoma	45-93
Urothelial	28-100
Multiple myeloma	93
Ovarian	33-80
Gastric carcinoma	42
Esophageal	42
Pancreatic	39
Renal cell carcinoma	15-24
Breast	31-34
Lymphomas	17-94*
Leukemias	11-42

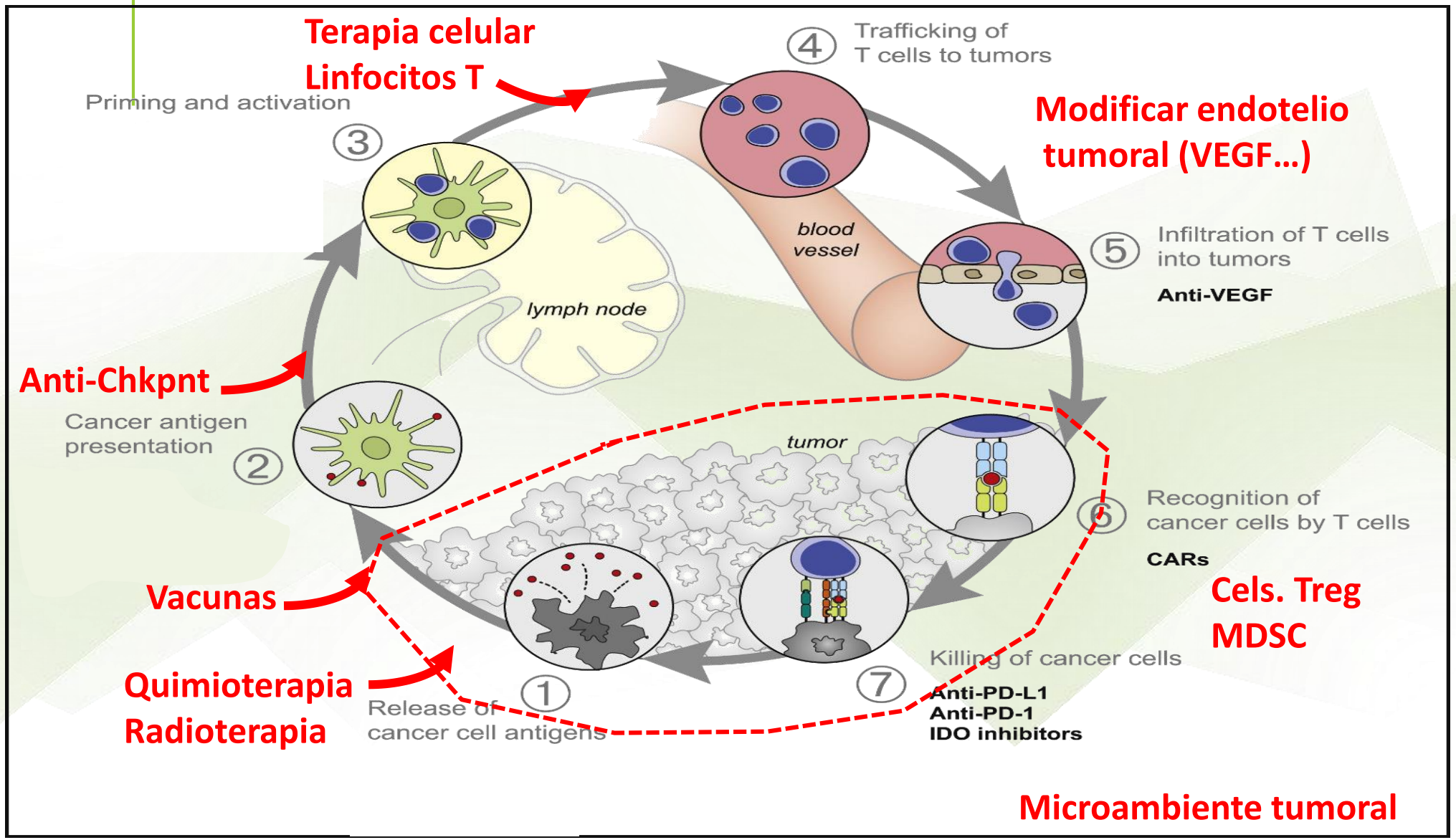






Sznol M, Chen L. Clin Cancer Res. 2013;

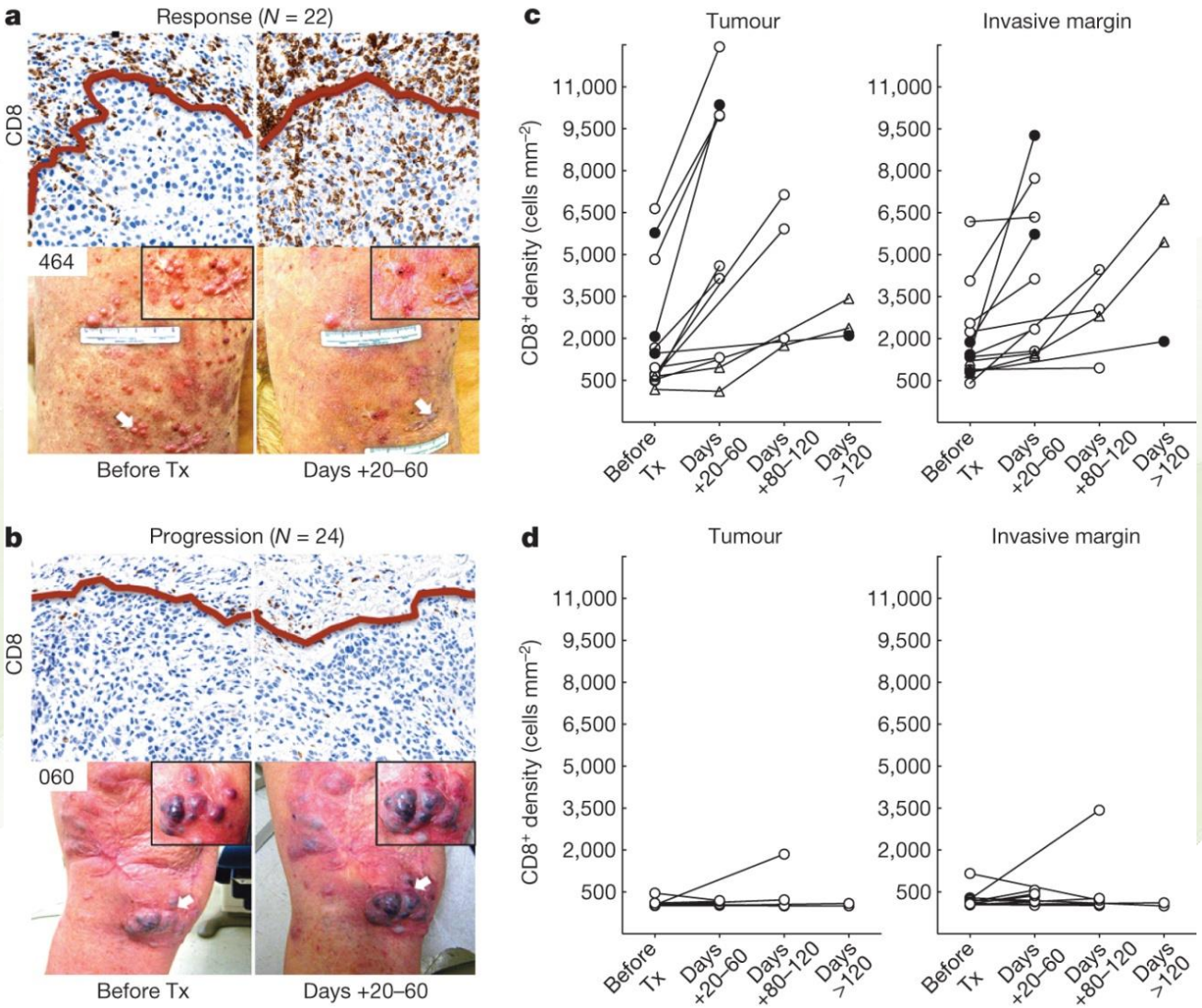
El ciclo "inmunidad-cancer". Estrategias terapéuticas



Toxicidades…

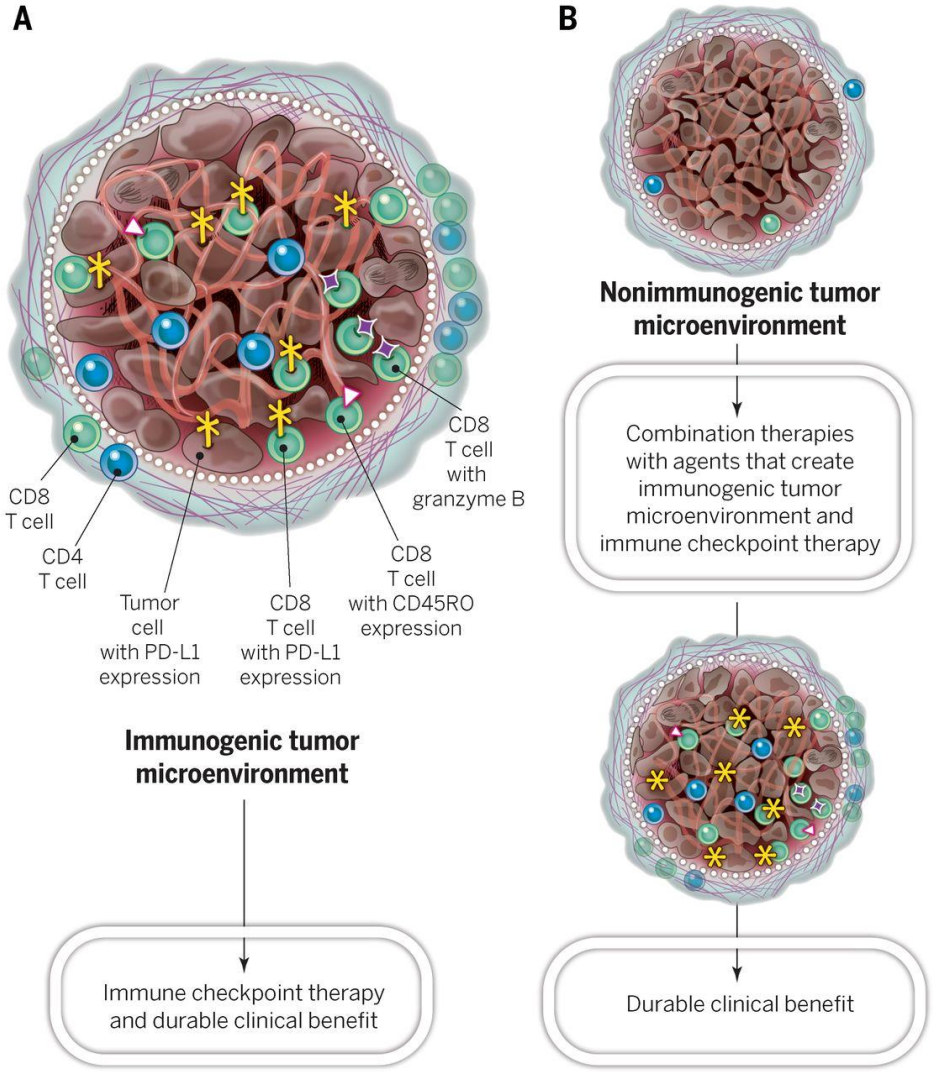
Chen and Mellman. Immunity. 2013

Análisis inmunohistoquímico de los linfocitos T CD8+ antes y durante el tratamiento con anti-PD-1

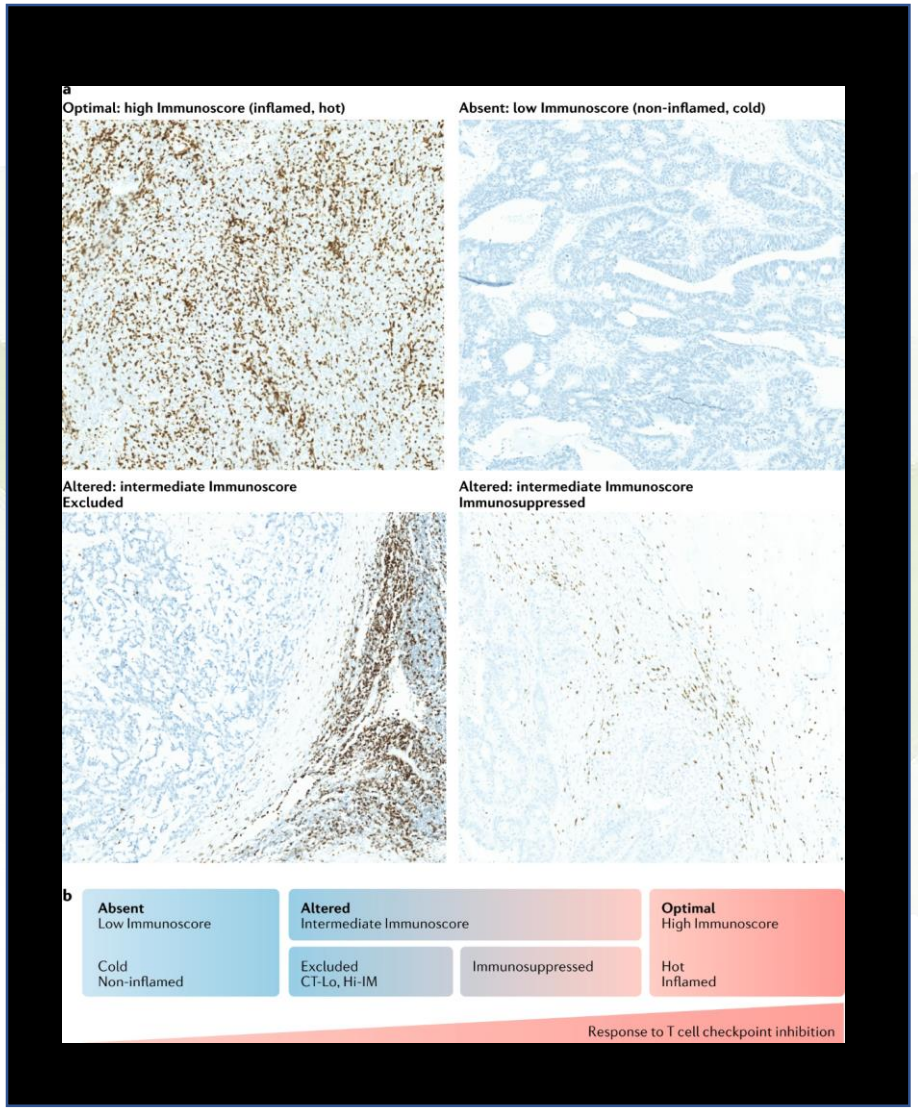


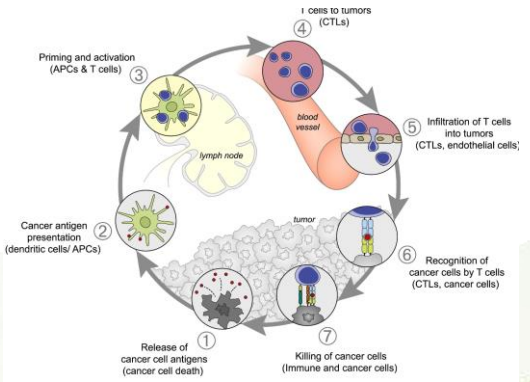
PC Tumeh *et al. Nature* **515**, 568-571 (2014) doi:10.1038/nature13954

Tumores inmunogénicos y no inmunogénicos



Sharma, Allison, Science, 2015:





Galon and Bruni,Nat Rev Drug Discov. 2019

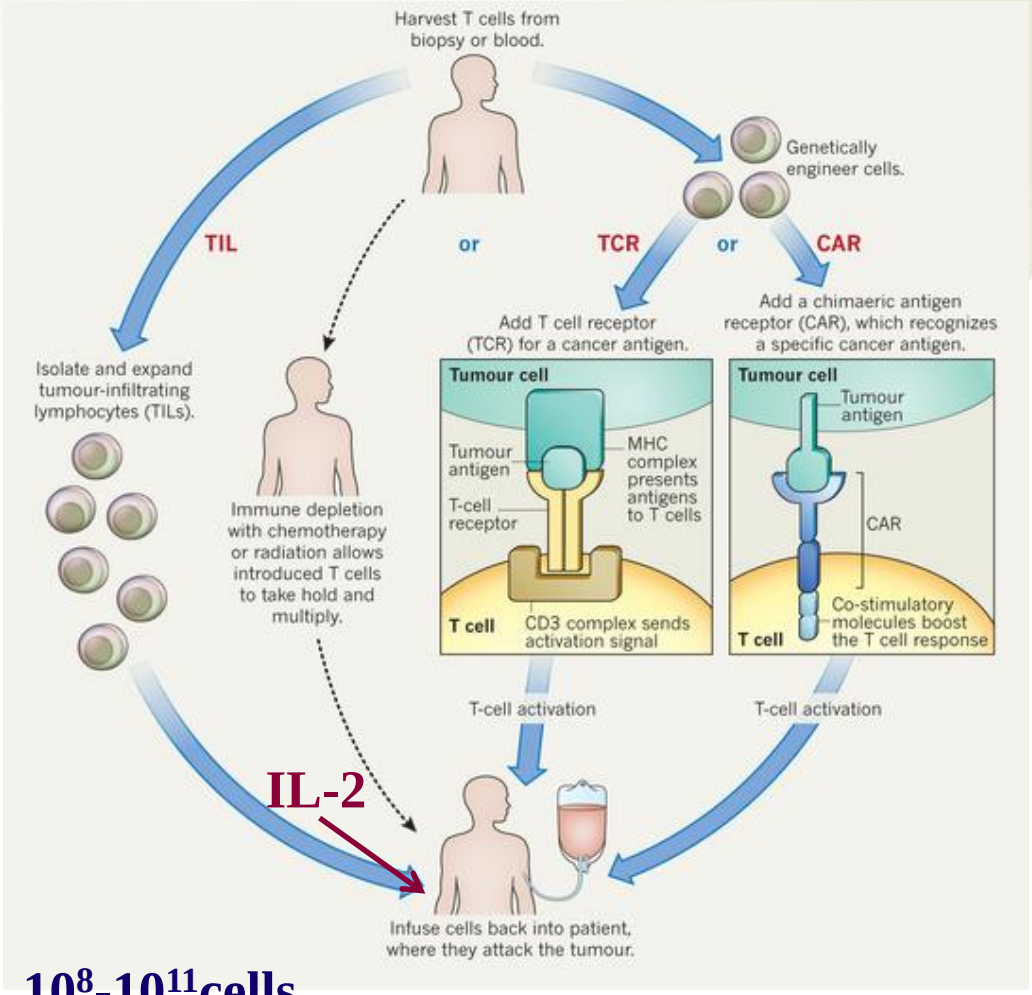
Terapia celular adoptiva

Naturally-ocurring tumor-specific T cells

TILs
(tumor-infiltrating lymphos)

ACT-TIL

Requerimientos
↑ Hot-tumor(Neo_antígenos)
Tumores resecables



10^8-10^{11}cells

Gene modified T cells

Transgenic TCR
CAR

ACT-TCR
ACT-CAR

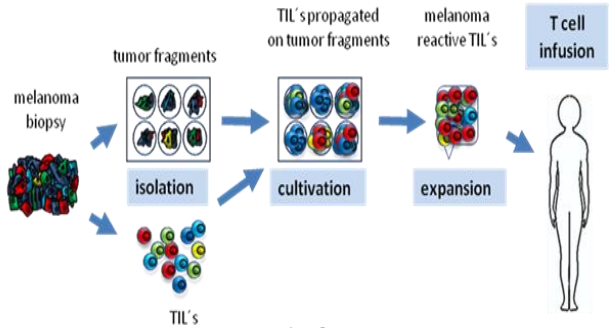
Nature (2013); 504:S13

TIL THERAPY
First clinical trial

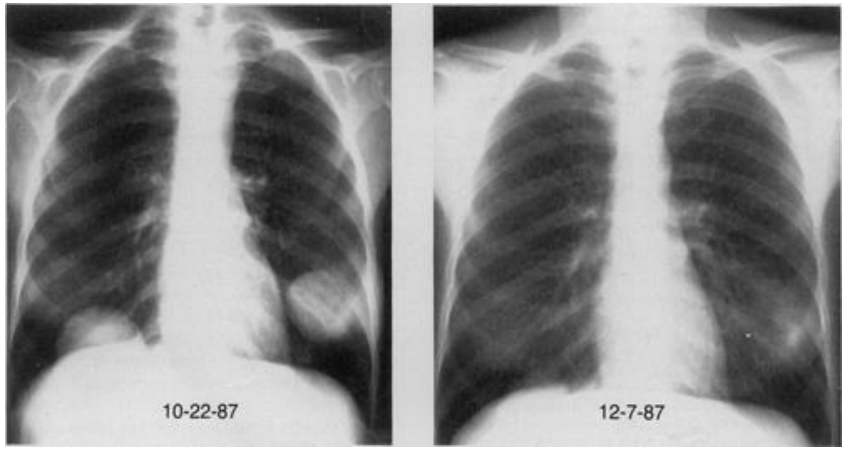
Use of Tumor-Infiltrating Lymphocytes and Interleukin-2 in the Immunotherapy of Patients with Metastatic Melanoma

Steven A. Rosenberg, M.D., Ph.D., Beverly S. Packard, Ph.D., Paul M. Aebersold, Ph.D., Diane Solomon, M.D., Suzanne L. Topalian, M.D., Stephen T. Toy, Ph.D., Paul Simon, Ph.D., Michael T. Lotze, M.D., James C. Yang, M.D., Claudia A. Seipp, R.N., Colleen Simpson, R.N., Charles Carter, Steven Bock, M.D., Douglas Schwartzentruber, M.D., John P. Wei, M.D., and Donald E. White, M.S.

N Engl J Med 1988; 319:1676-1680 | December 22, 1988 | DOI: 10.1056/NEJM198812223192527



+IL2
Preconditioning_ ciclofosfamida



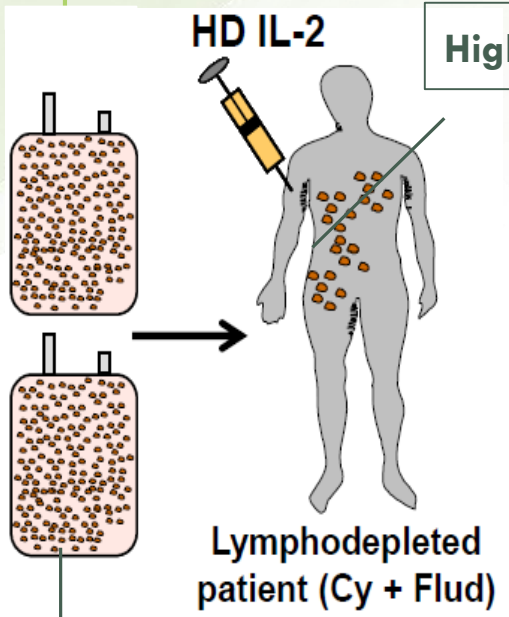
11/20 (55%)

Abstract

Lymphocytes extracted from freshly resected melanomas can be expanded in vitro and can often mediate specific lysis of autologous tumor cells but not allogeneic tumor or autologous normal cells. We treated 20 patients with metastatic melanoma by means of adoptive transfer of these tumor-infiltrating lymphocytes and interleukin-2, after the patients had received a single intravenous dose of cyclophosphamide. Objective regression of the cancer was observed in 9 of 15 patients (60 percent) who had not previously been treated with interleukin-2 and in 2 of 5 patients (40 percent) in whom previous therapy with interleukin-2 had failed. Regression of cancer occurred in the lungs, liver, bone, skin, and subcutaneous sites and lasted from 2 to more than 13 months. Toxic effects of interleukin-2 occurred, although the treatment course was short (five days); these side effects were reversible.

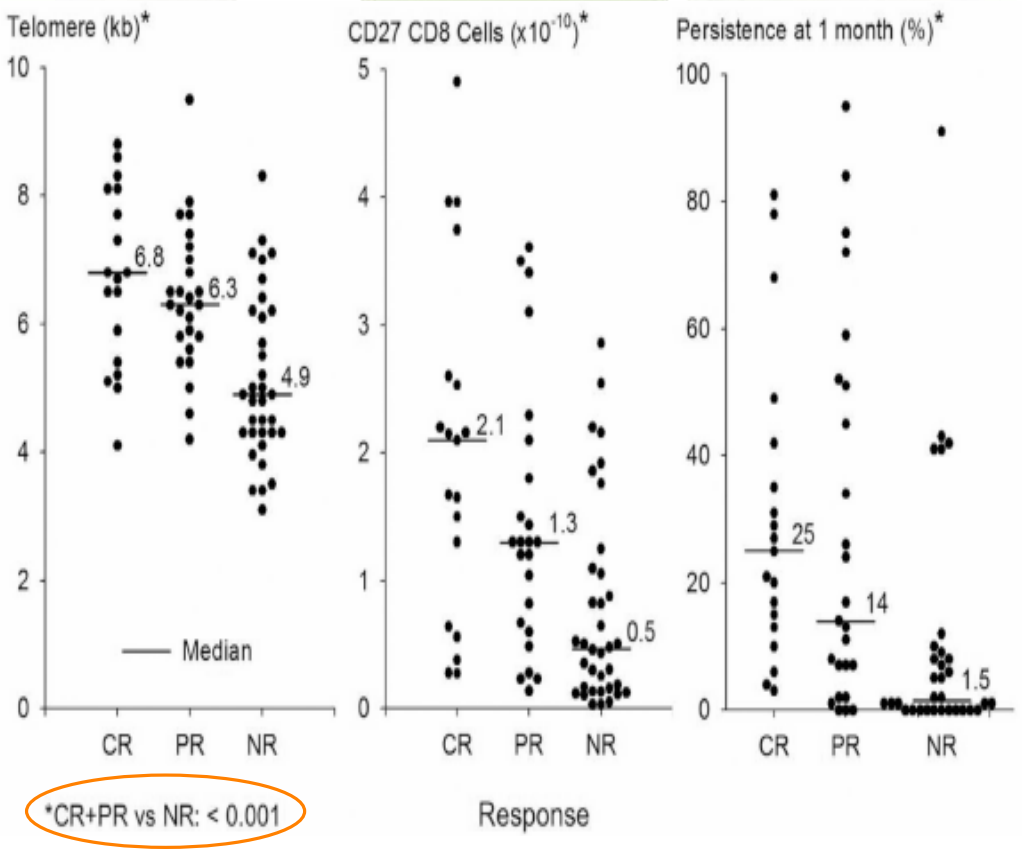
It appears that in patients with metastatic melanoma, this experimental treatment regimen can produce higher response rates than those achieved with interleukin-2 administered alone or with lymphokine-activated killer cells. It is too early to determine whether this new form of immunotherapy can improve survival, but further trials seem warranted.

Factores asociados a la respuesta a la terapia con TIL



High persistence of TILs at 1 month

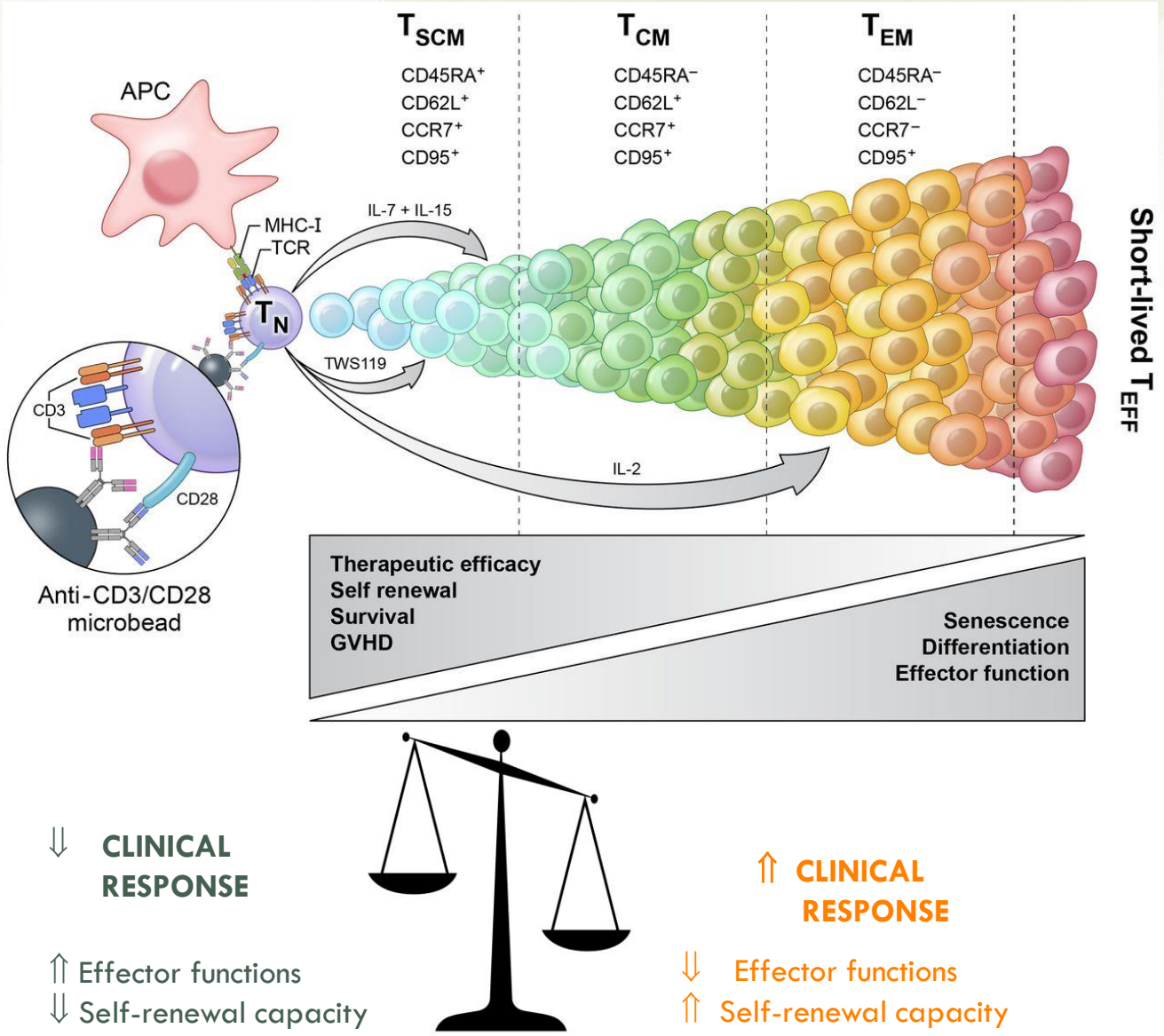
-High number of CD27$^+$ CD28$^+$ T cells -Long telomers



Rosenberg, SA. Clin Cancer Res. 2011

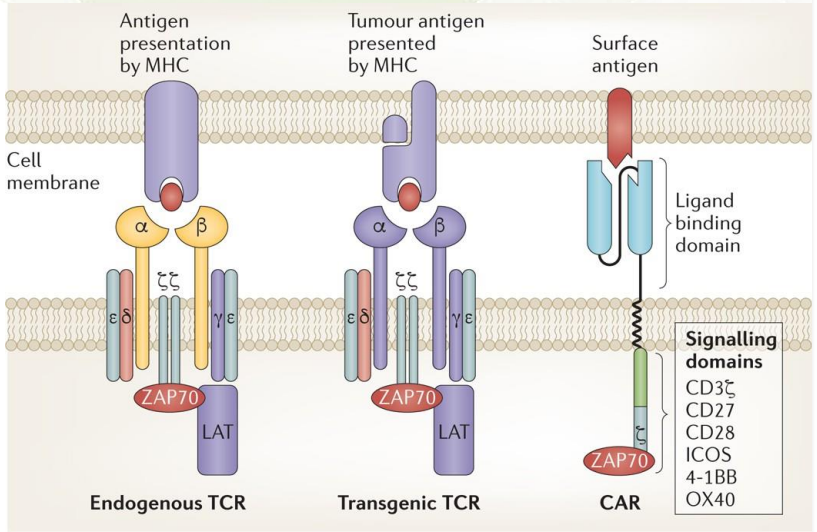
Estado de diferenciación de los TIL y eficacia terapéutica

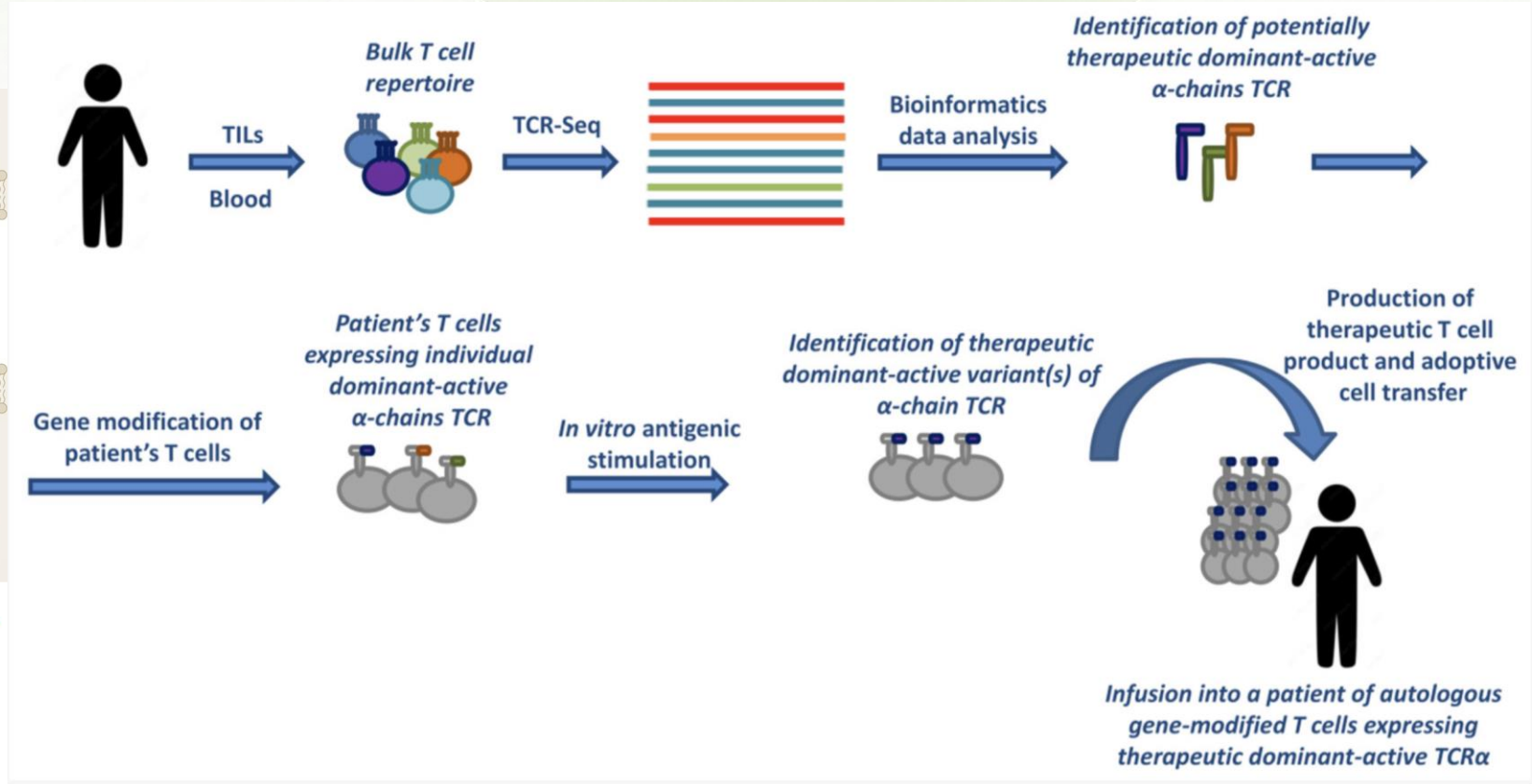
TN: naive
TSCM: stem cell memory
TCM: central memory T cell
TEM: effector memory T cell
TEFF: effector T cell



Nat Rev Cancer 2012

Terapia adoptiva de células T basada en TCR transgénicos





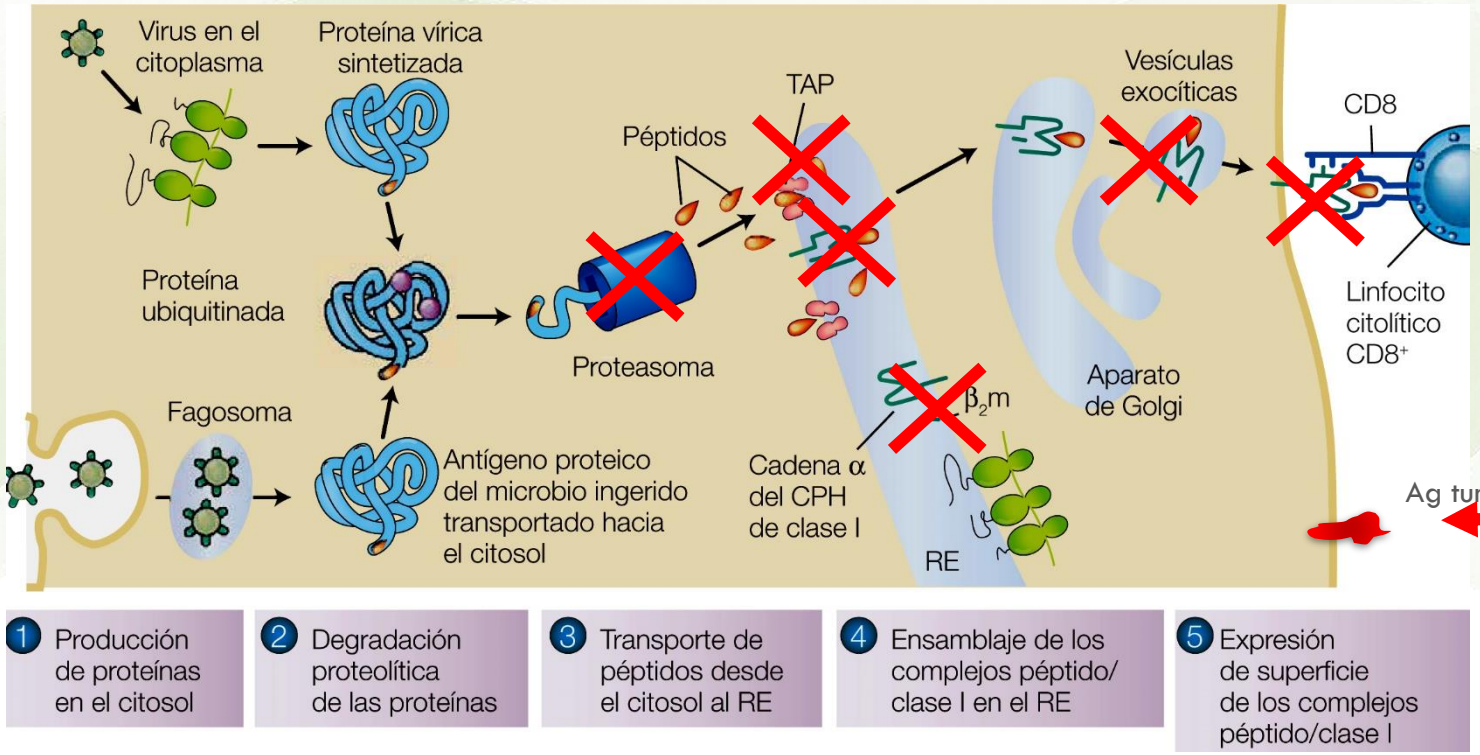
Kalanina et al, Int. J. Mol. Sci. 2023

Ensayos clínicos de Terapia adoptiva de células T basada en TCR transgénicos

Target antigen	HLA	Cancer type	Clinical trial	(ORR) (%)	Clinical response
MART-1	HLA-A*0201	Melanoma	n.s	2/17 (12)	2 PR
MART-1	HLA-A*02:01	Melanoma	NCT00509288	6/20 (30)	6PR
MART-1	HLA-A*02:01	Melanoma	NCT00910650	0/13 (0)	0
MART-1	HLA-A*02:01	Melanoma	NCT02654821	2/12 (16.7)	2PR
gp100	HLA-A*02:01	Melanoma	NCT00509496	3/16 (16)	1CR, 2PR
CEA	HLA-A*02:01	Colorectal cancer	NCT00923806	1/3 (33)	1PR
NY-ESO-1	HLA-A*02:01	Melanoma; synovial sarcoma	NCT00670748	5/11 (45) 4/6 (67)	2CR, 3PR; 4PR
NY-ESO-1	HLA-A*02:01	Melanoma; synovial sarcoma	NCT00670748	11/20 (55); 11/18 (61)	4CR, 7PR; 1CR, 10PR
NY-ESO-1	HLA-A*02:01	Melanoma; synovial sarcoma; liposarcoma; osteosarcoma; MPNST	NCT02070406; NCT01697527	2/10 (20)	2PR
NY-ESO-1	HLA-A*02:01 ; HLA-A*02:06	Synovial sarcoma	NCT01343403	6/12 (50)	1CR, 5PR
NY-ESO-1	HLA-A*02:01, HLA-A*02:06	Synovial sarcoma	NCT01343403	9/30 (30)	9PR
NY-ESO-1	HLA-A*02:01, HLA-A*02:06	Synovial sarcoma	JMA-IIA00346	1/3 (33)	1CR
NY-ESO-1 (CRISPR/Cas9)	HLA-A*02:01	Metastatic sarcoma; Myeloma	NCT03399448	0/3 (0)	0
NY-ESO-1	HLA-A*02:01	Myeloma	NCT01352286	11/25 (44)	1SCR, 1CR, 8VGPR, 1PR
MAGE-A3	HLA-A*02:01	Melanoma; synovial sarcoma; esophageal cancer	NCT01273181	5/9 (56)	1CR, 4PR
MAGE-A3	HLA-A*01	Melanoma	NCT01350401	0/1 (0)	0
MAGE-A3	HLA-DPB1*0401	Metastatic solid tumors	NCT02111850	4/17 (23.5)	1CR, 3PR
MAGE-A4	HLA-A*24:02	Esophageal cancer	UMNII000002395	0	/
MAGE-A4	HLA-A*02	Relapsed/refractory metastatic solid tumors (9 types)	NCT03123922	9/38 (24)	9PR
MAGE-10	HLA-A*02:01 OR HLA-A*02:06	Nsclc	NCT02592577	1/11 (9)	1PR

PRESENTACIÓN ANTIGÉNICA: RECONOCIMIENTO DEL AG EN EL TUMOR.

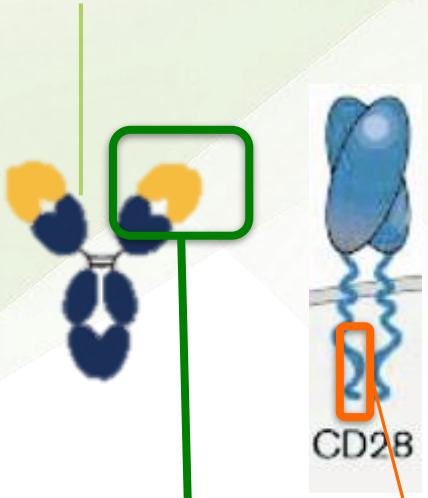
Problemas que aparecen en la maquinaria de presentación en el cáncer

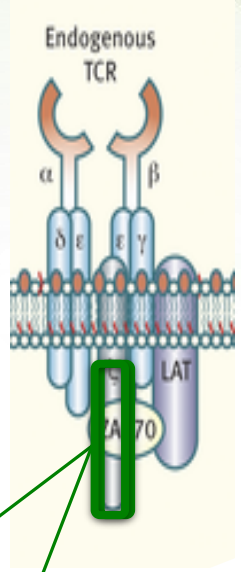


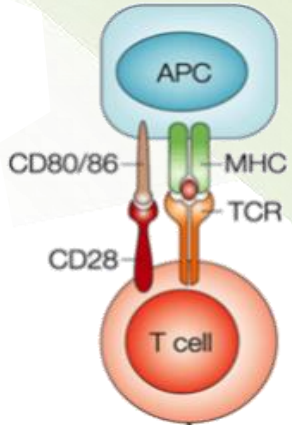
•Carcinoma colorectal, vejiga, ovario meduloblastoma, leucemia mieloide aguda carcinoma de cabeza y cuello, esófago, estómago, cervix, astrocitoma, próstata, melanoma…

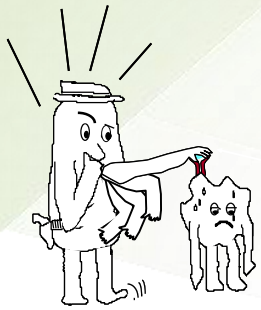
Revisado en Leone P et al. JNCI J Natl Cancer Inst 2013;105:1172-1187

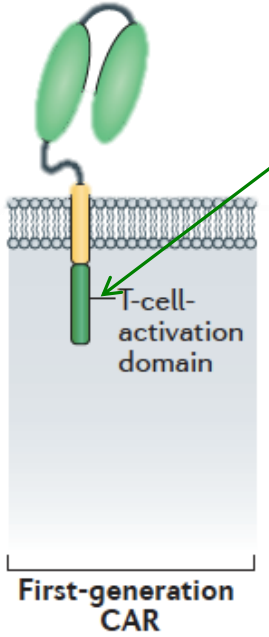
Linfocitos T redirigidos: CAR: Chimeric antigen receptors





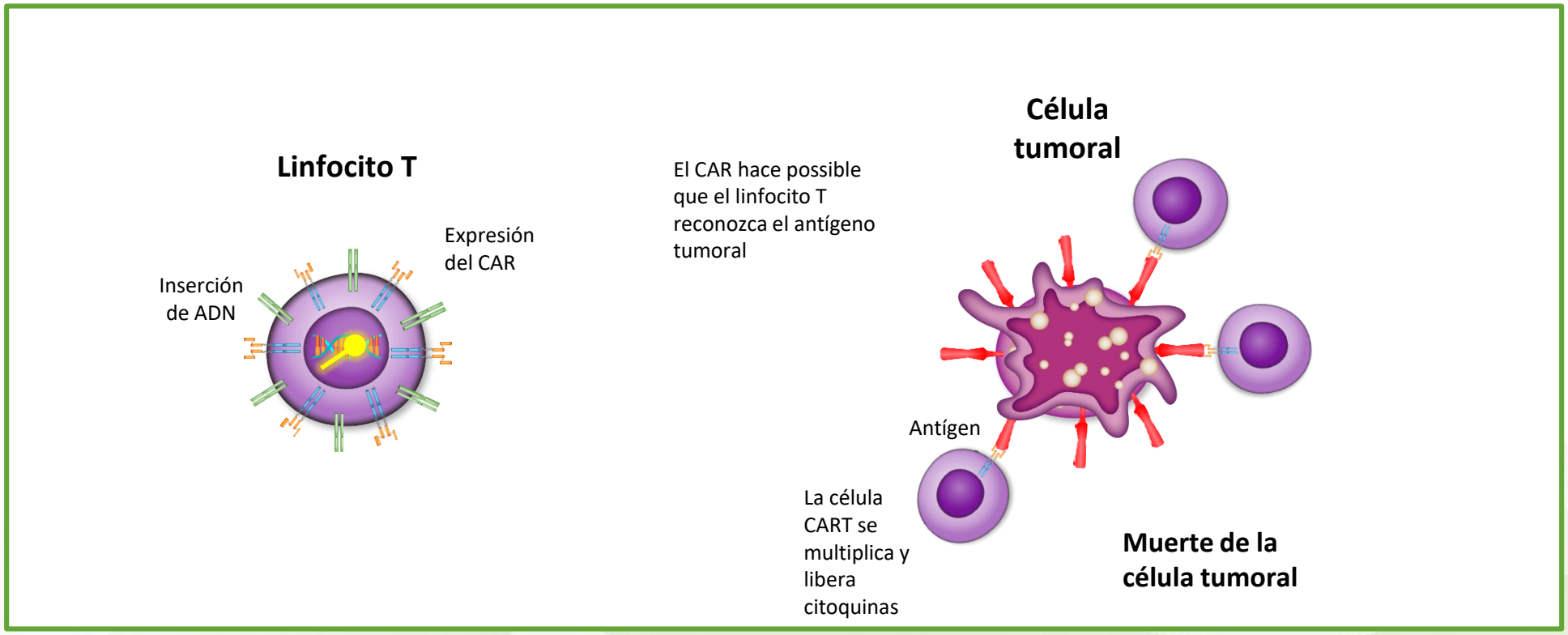




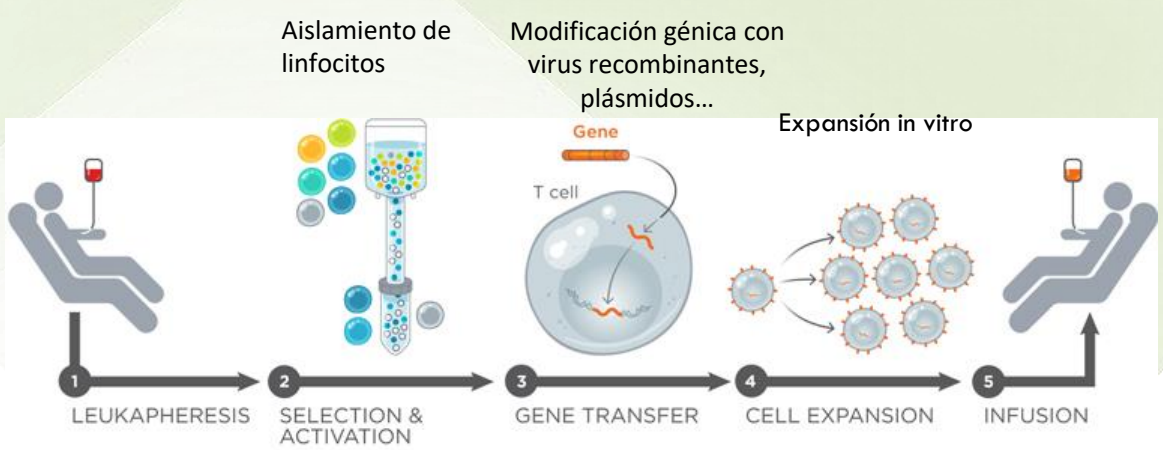


Brudno and Kochenderfer. Nat Rev Clin Oncol 2017

CAR T CELLS: MECANISMO DE ACCIÓN



Proceso de preparación de los CAR-T cells



Resultados clínicos de la terapia CAR-T

CD19 CAR-T cells

KYMRIAH® (tisagenlecleucel) Dispersion for IV infusion

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

Breyanzi™ (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

BCMA CAR-T cells

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

CARVYKTI™ (ciltacabtagene autoleucel) Suspension for IV Infusion

TABLE 2. Commercial and Advanced CAR T-Cell Outcomes

Name	Reference	Patients	Responses	Survival
Pediatric and Young Adult (≤ 25 years) Patients With R/R Acute Lymphoblastic Leukemia				
Tisagenlecleucel	Pivotal ELIANA[1]	92 enrolled, 75 treated	Per protocol: CR/CRi, 81% at 3 months	Per protocol: EFS, 50%; OS, 76% (12 months)
Tisagenlecleucel	Real world[2]	255 treated	CR, 86%	EFS, 52%; OS, 77% (12 months)
R/R Large B-Cell Lymphoma				
Axicabtagene ciloleucel	Pivotal ZUMA-1[3]	111 enrolled, 101 treated	ORR, 82%; CR, 58%	PFS, 44% (12 months); OS, 52% (18 months)
Axicabtagene ciloleucel	Real world[4]	275 treated	ORR, 82%; CR, 64%	PFS, 45%; OS, 64% (12 months)
Axicabtagene ciloleucel	Real world[50]	122	ORR, 70%; CR 50%	OS, 57% (12 months)
Tisagenlecleucel	Pivotal JULIET[5]	165 enrolled, 93 treated	ORR, 52%; CR, 40%	RFS, 65%; OS, 49% (12 months)
Tisagenlecleucel	Real world[2]	155 treated	ORR, 62%; CR, 40%	PFS, 39%; OS, 71% (6 months)
Lisocabtagene maraleuecel	Pivotal TRANSCEND NHL001[51]	344 apheresed, 269 treated, 256 evaluable for efficacy	ORR, 73%; CR, 53%	PFS, 44%; OS, 58% (12 months)
Mantle Cell Lymphoma				
Brexucabtagene autoleucel	Pivotal ZUMA-2[79]	74 enrolled, 68 treated	ORR, 93%; CR, 67%	PFS, 61%; OS, 83% (12 months)
R/R Follicular Lymphoma				
Axicabtagene ciloleucel	Pivotal ZUMA-5[20]	123 treated (follicular lymphoma only)	ORR, 94%; CR, 80%	PFS, 74%; OS, 93% (12 months)
Multiple Myeloma (BCMA)				
Idecabtagene vicleucel	Pivotal KarMMa[115]	140 enrolled, 128 treated (dose escalation)	ORR, 73%; CR, 33%; MRD-ve, 26%	Median PFS, 8.8 months; OS 78% (12 months)

Abbreviations: CR, complete response; CRi, CR with incomplete hematologic recovery; EFS, event-free survival; MRD-ve, minimal residual disease negative; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; R/R, relapsed/refractory.

Gill, S., and Brudno, J.N. (2021). Am. Soc. Clin. Oncol. Educ. B., e246–e265.

Terapia CAR-T en tumores sólidos

1. **Severos efectos on-target, off-tumor**
   Falta de un antígeno único para generar CAR-T altamente específicos

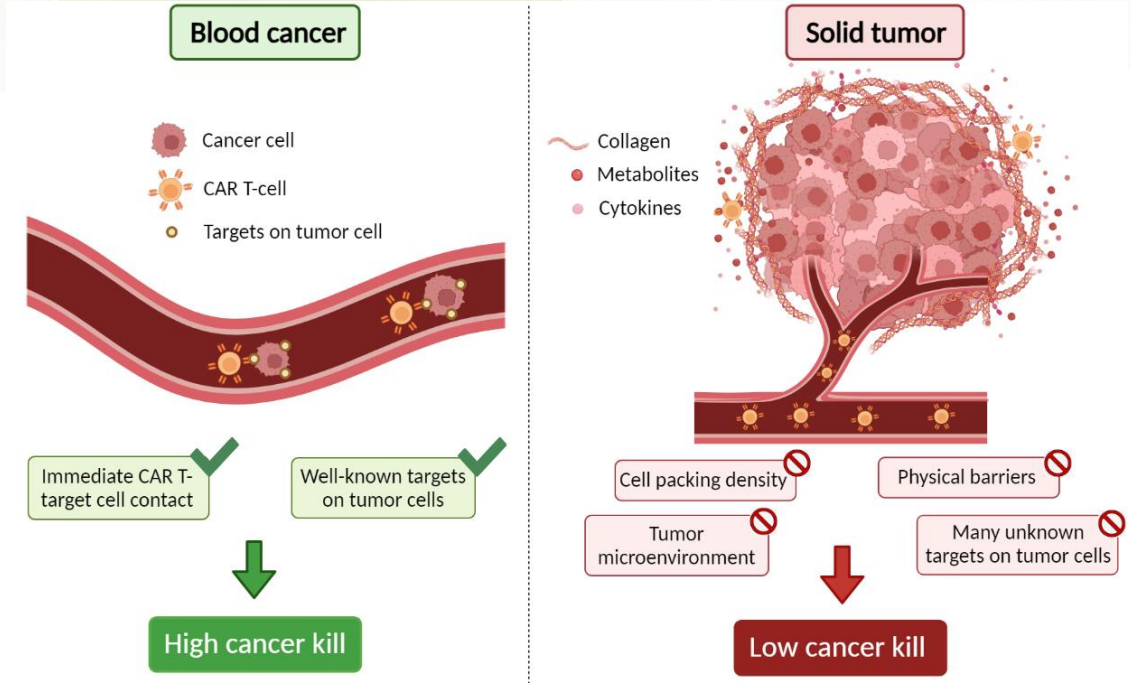
2. **Expresión heterogénea** del antígeno diana

3. **Barreras físicas, matriz extracelular**

4. **Resistencia a la presión inmunológica adaptativa**
   1. PDL-1, IDO

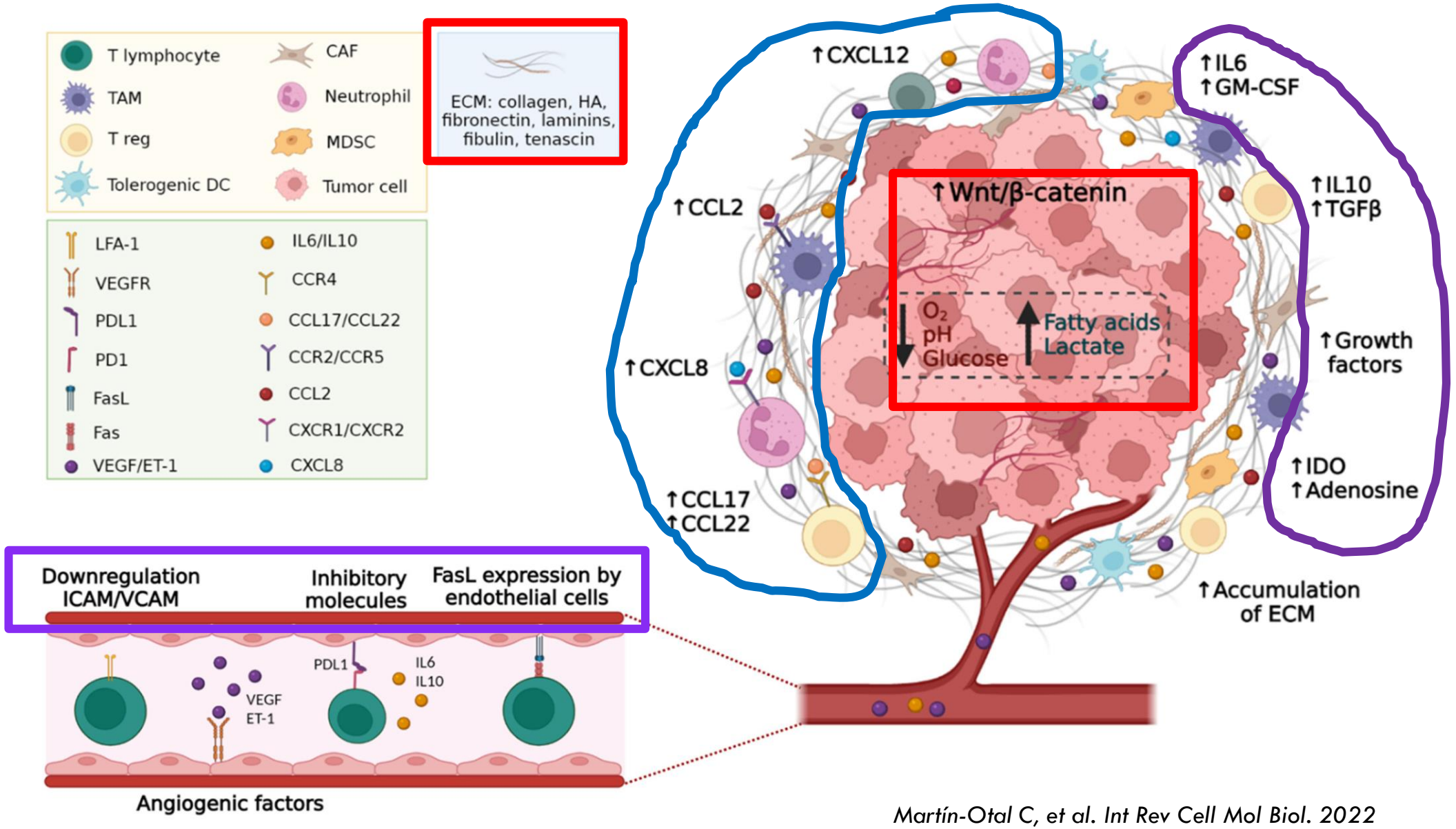
5. **Ineficiente homing** de los linfocitos al tumor
   1. Falta de expresión de quemoquinas en el tumor que atraigan a los linfocitos
   2. El tumor expresa factor angiogénicos (VEGF, FGFs, ET-1..)

6. Existencia de un **microambiente hostil** para la acción de los linfocitos
   A. Treg, MDMS, M2, citoquinas inmunosupresoras(TGF-β, IL-10, ADO)
   B. Cambios metabólicos



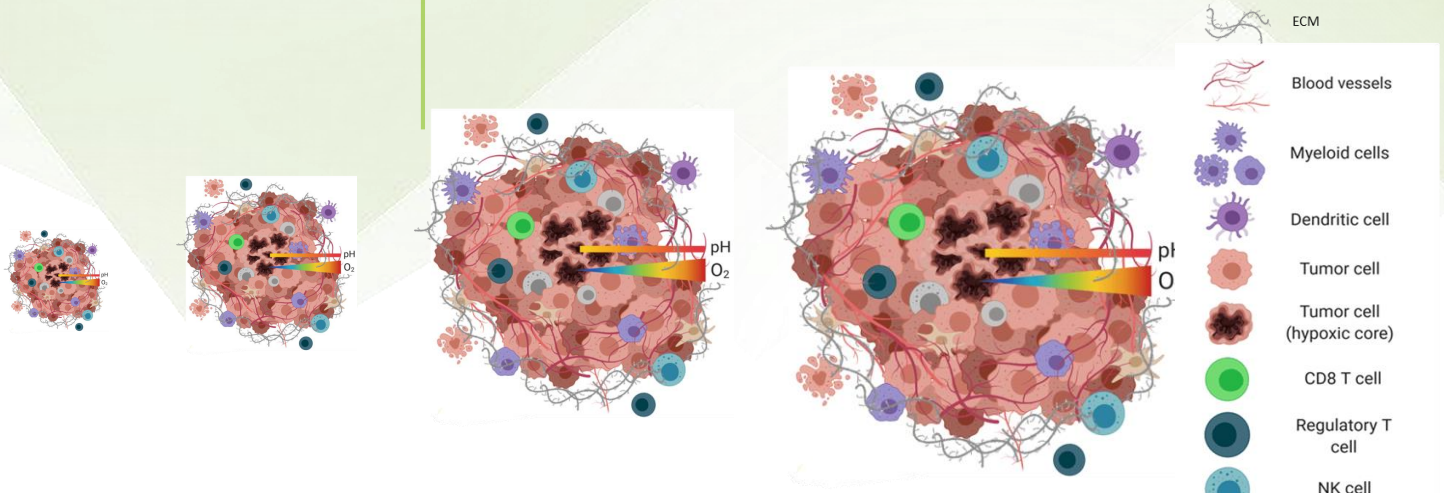
Jessica Hartmann et al.
EMBO Mol Med. 2017;emmm.201607485

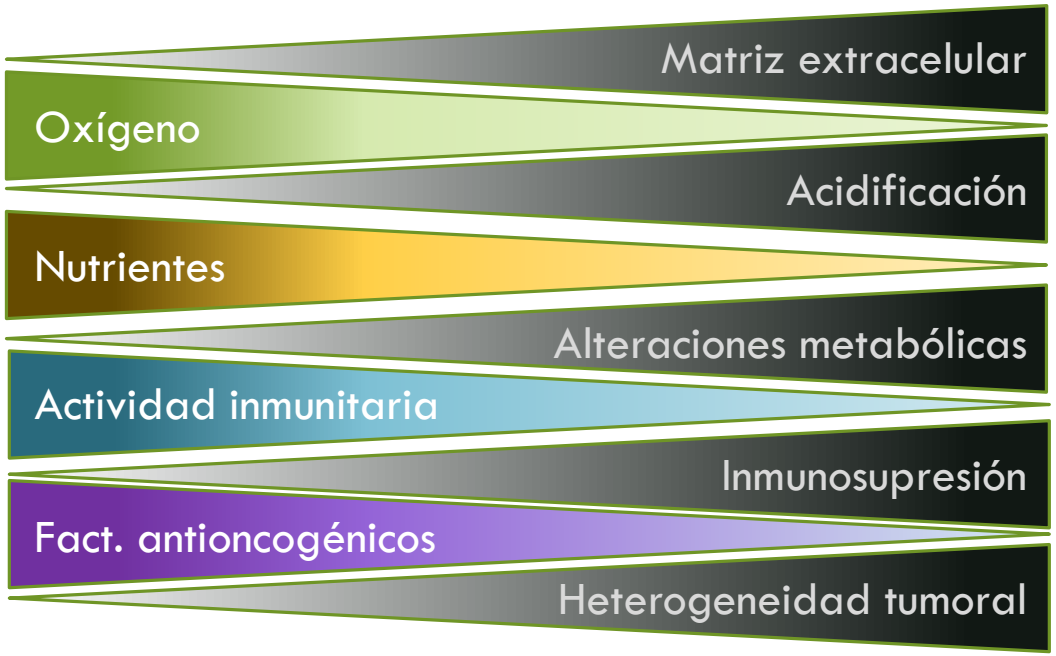
Efecto del microambiente tumoral sobre el Sistema inmunitario y las terapias celulares



Martín-Otal C, et al. Int Rev Cell Mol Biol. 2022

Dinámica del microambiente tumoral.
Dificultades de las terapias celulares adotivas en tumores sólidos





Dificultades

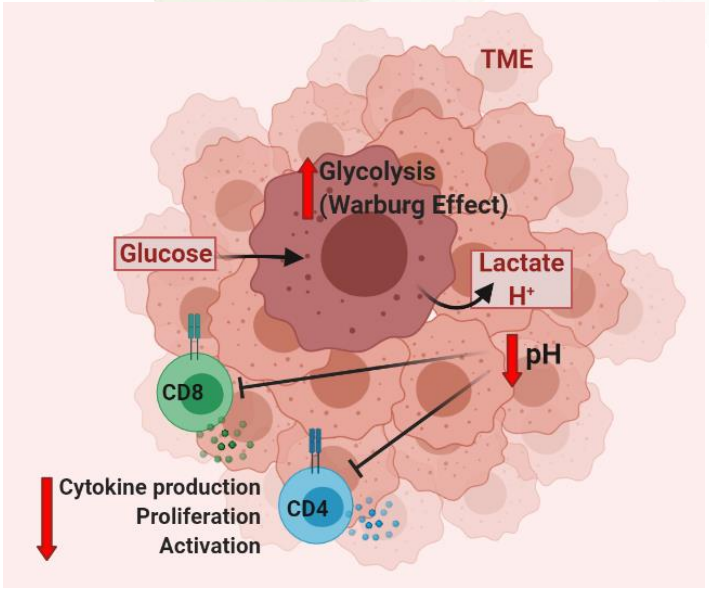
- Falta de antígenos específicos?
- Barreras físicas que impiden en tráfico linfocitoario en el tumor
- Vasculatura aberrante
- Ambiente inmunosupresor

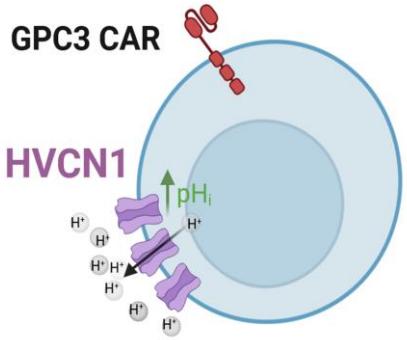
EL MICROAMBIENTE TUMORAL ACÍDICO (TME) INHIBE LA FUNCIONALIDAD DE LOS LINFOCITOS

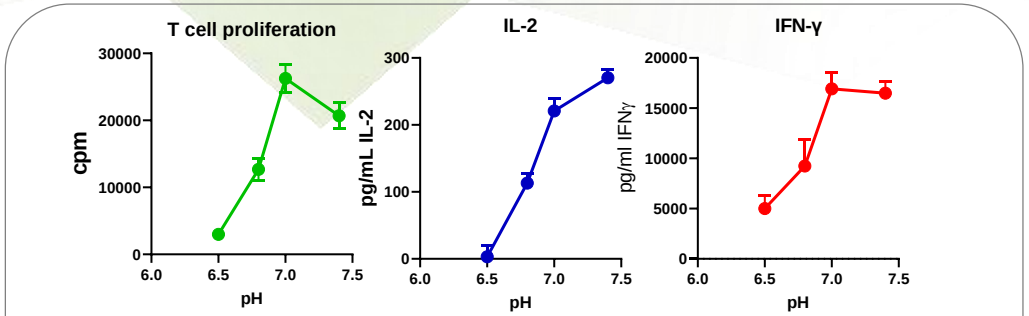
Dificultad

- pH acídico del microambiente tumoral

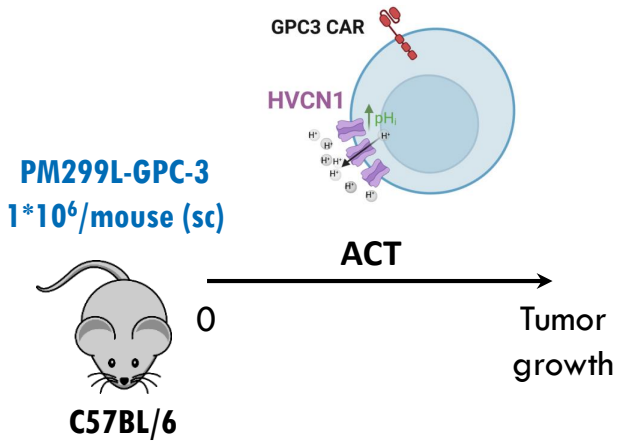
- El alto ritmo glicolítico de las células tumorales resulta en la acidificación del pH
- El pH acídico inhibe la activación de las células T,

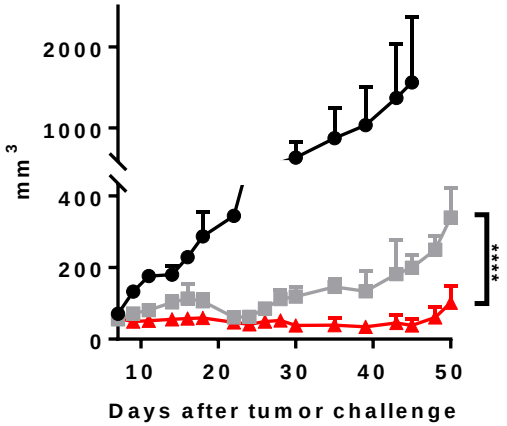






Qué podemos hacer para que los linfocitos T resistan el pH acídico del tumor?

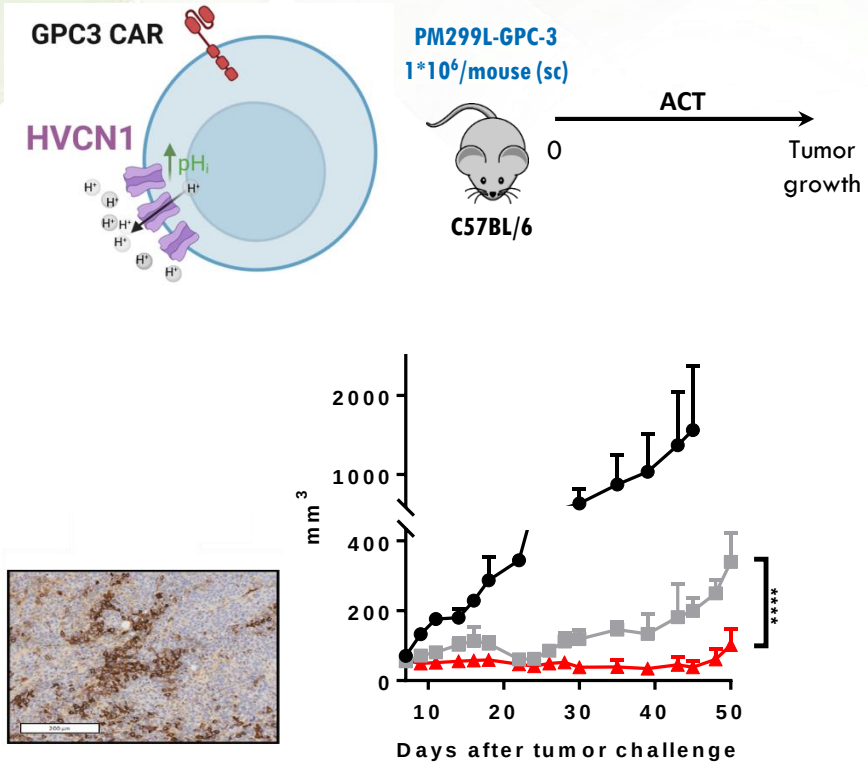




Navarro et al. Oncoimmunology, 2022

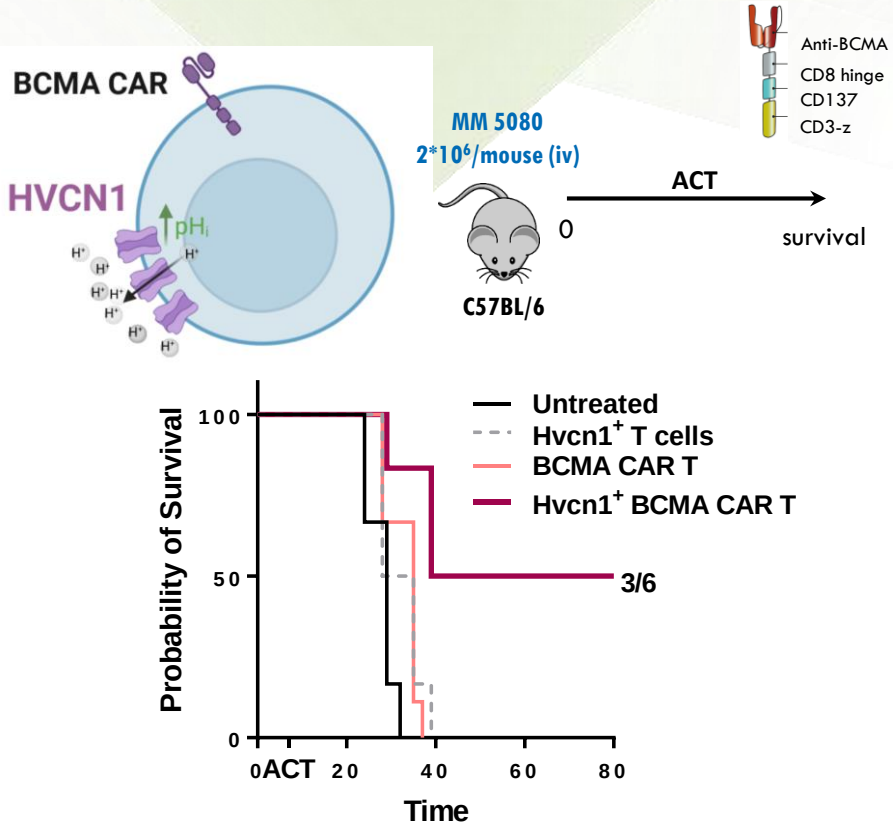
LA SOBREEXPRESIÓN DE HVCN1 MEJORA LA INMUNOTERAPIA DE CÉLULAS T CON CAR EN MODELO DE MIELOMA MÚLTIPLE

Hepatocarcinoma model



Navarro et al. Oncoimmunology, 2022

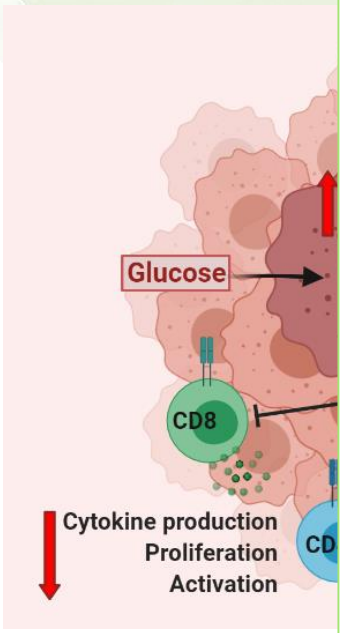
Multiple myeloma model



Unpublished,

Elementos del microambiente tumoral que afectan la eficacia de las terapias de células T adoptivas

LA PRIVACIÓN DE NUTRIENTES EN EL TME INHIBE LA FUNCIÓN DE LAS CÉLULAS T: GLUTAMINA



Qué podemos ha
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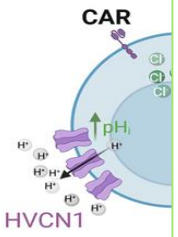

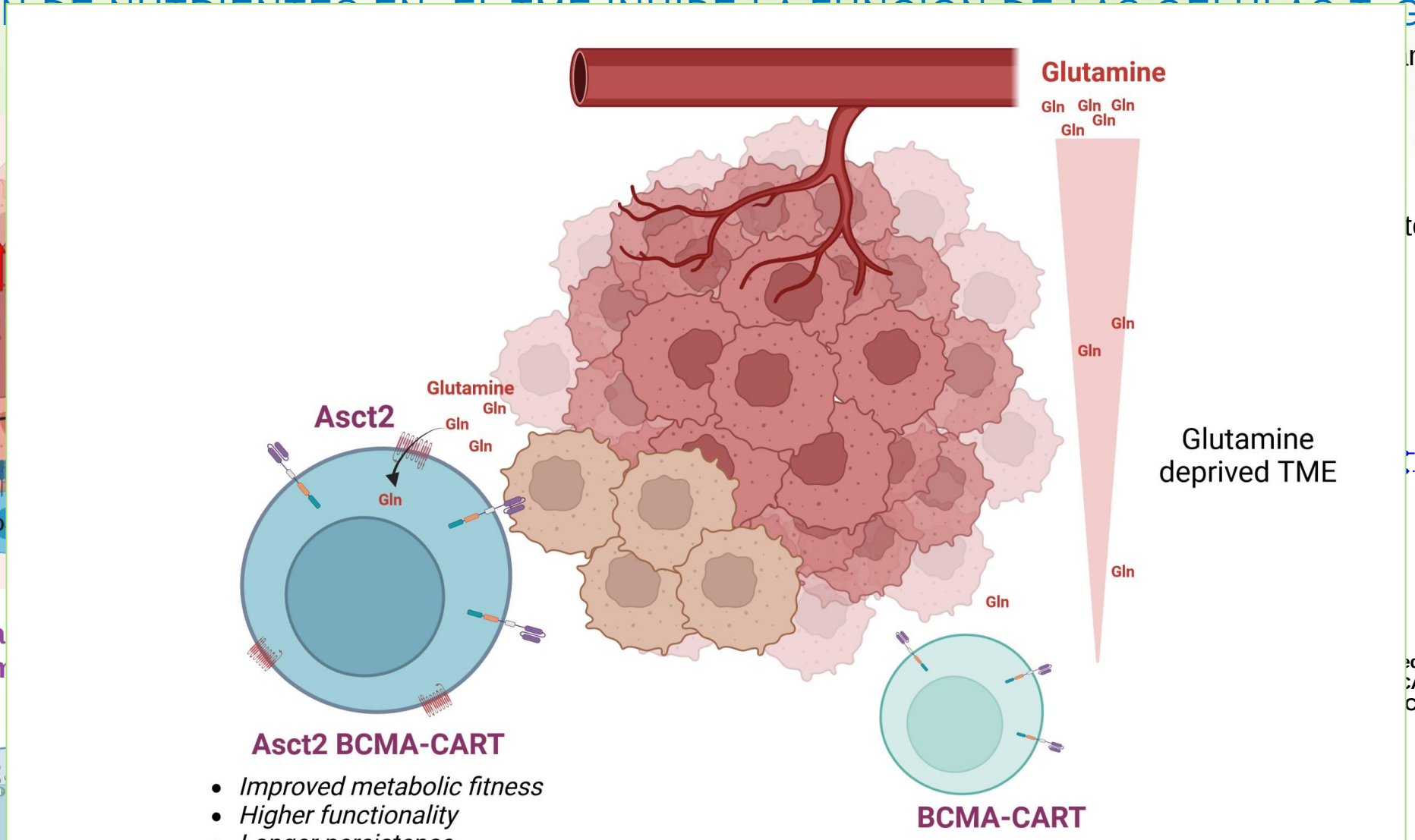

- *Improved metabolic fitness*
- *Higher functionality*
- *Longer persistence*

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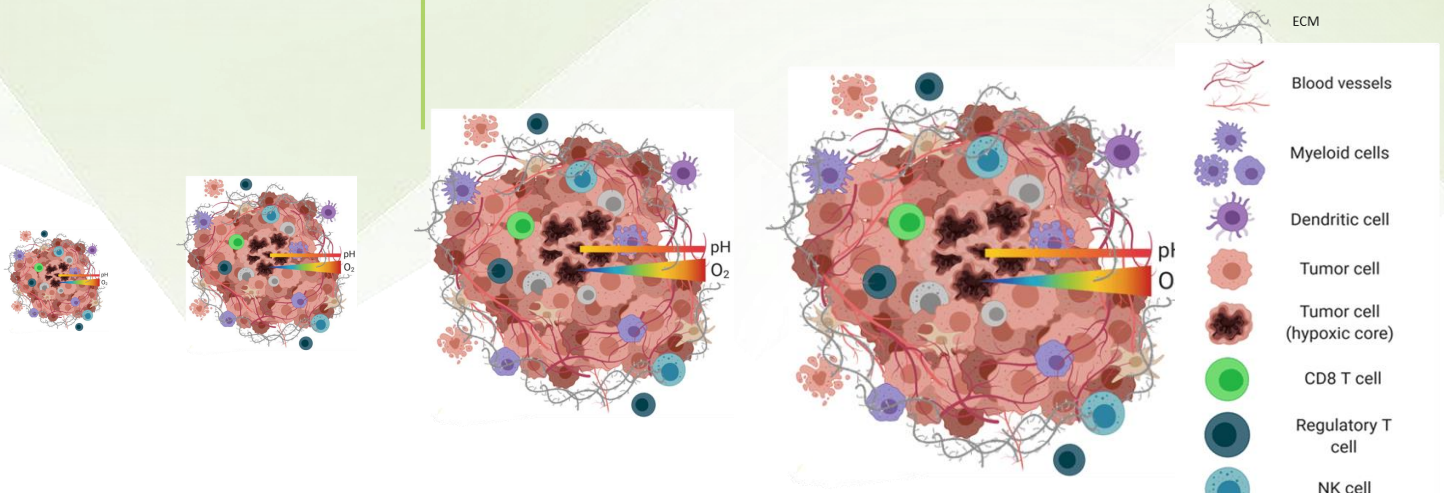
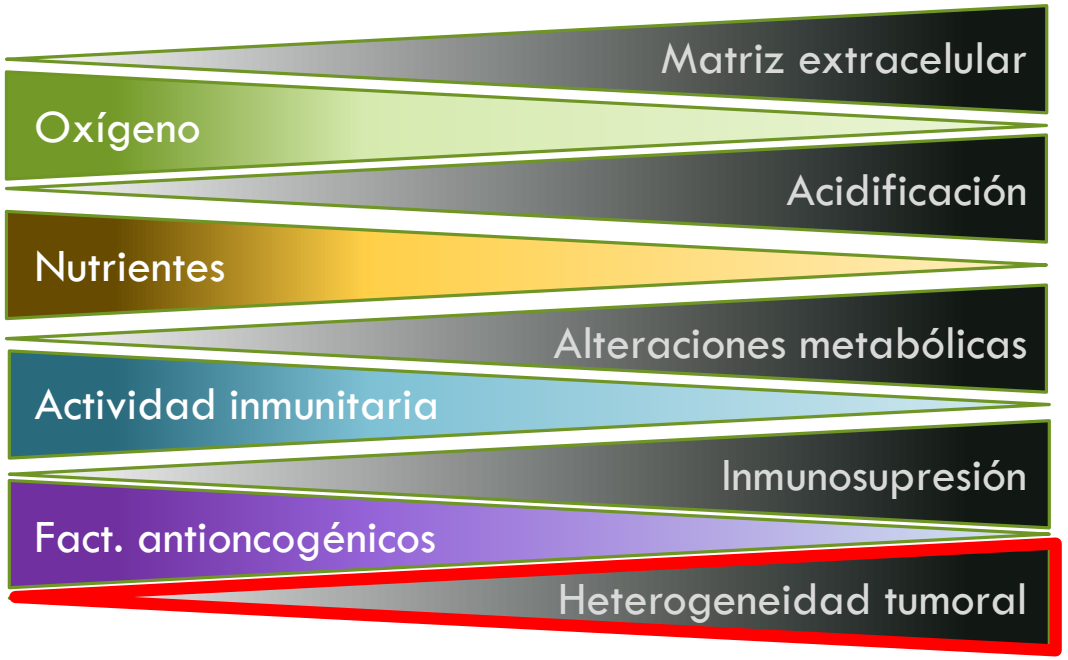
BCMA-CART (Stim)
Unstim BCMA-CART

ed (0/8)
CART (0/8)
CMA-CART (10/10)

nder review

Dinámica del microambiente tumoral.
Dificultades de las terapias celulares adotivas en tumores sólidos

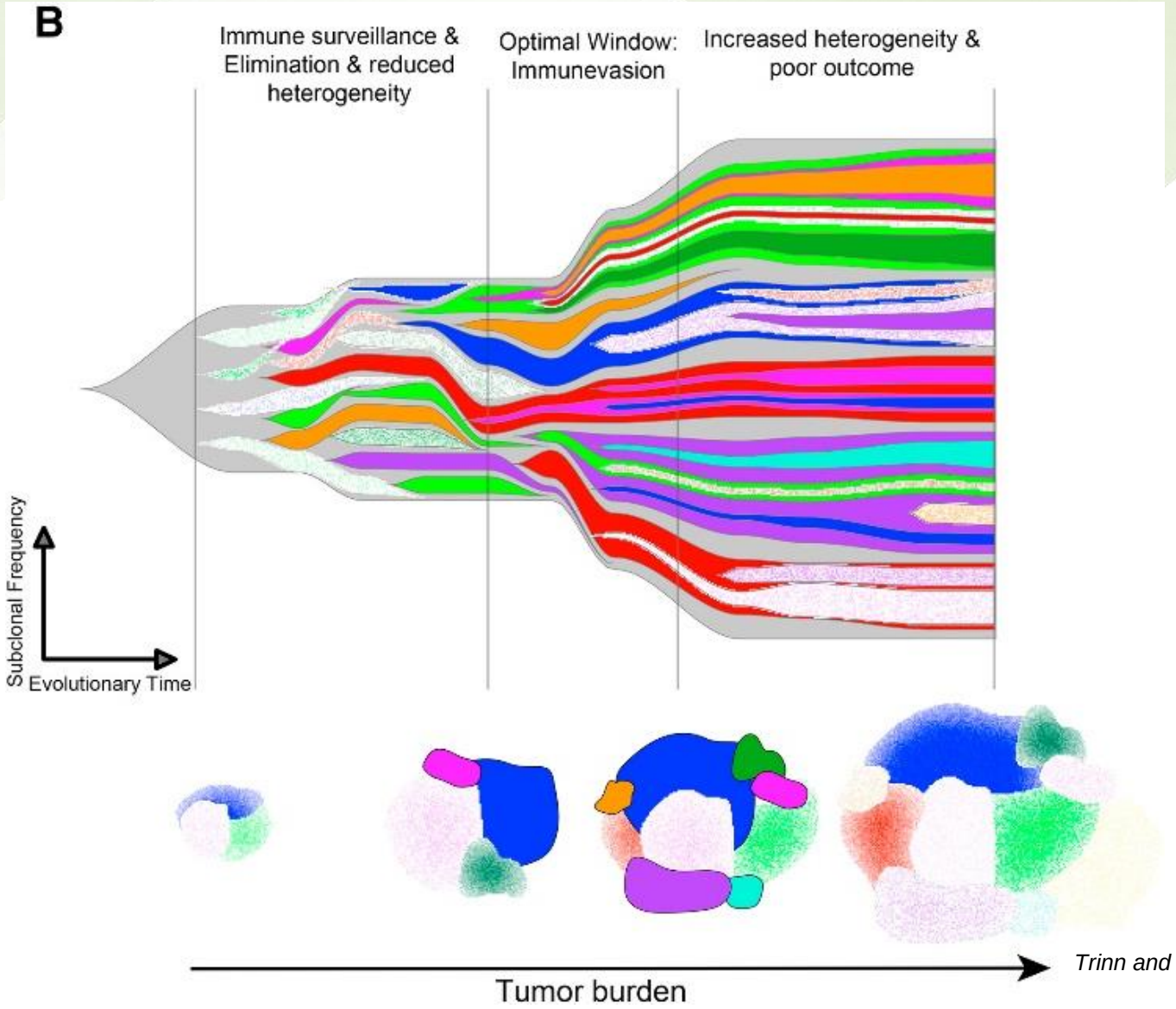




Dificultades

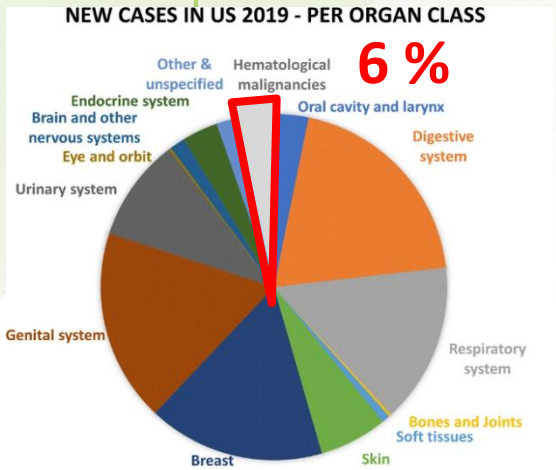
- Falta de antígenos específicos?
- Barreras físicas que impiden en tráfico linfocitoario en el tumor
- Vasculatura aberrante
- Ambiente inmunosupresor

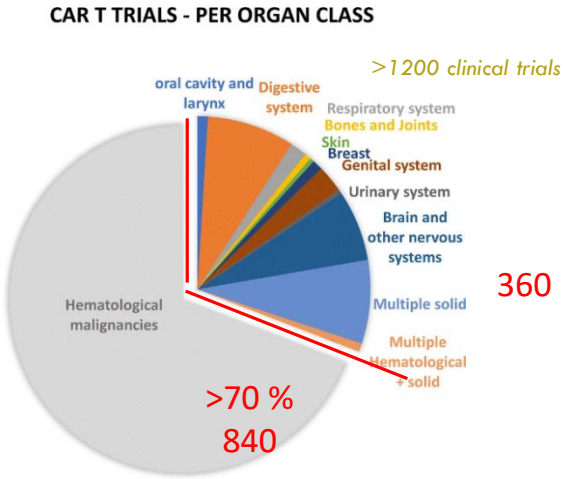
La heterogeneidad intratumoral impulsa la evolución tumoral y la respuesta a los inhibidores de puntos de control inmunitario



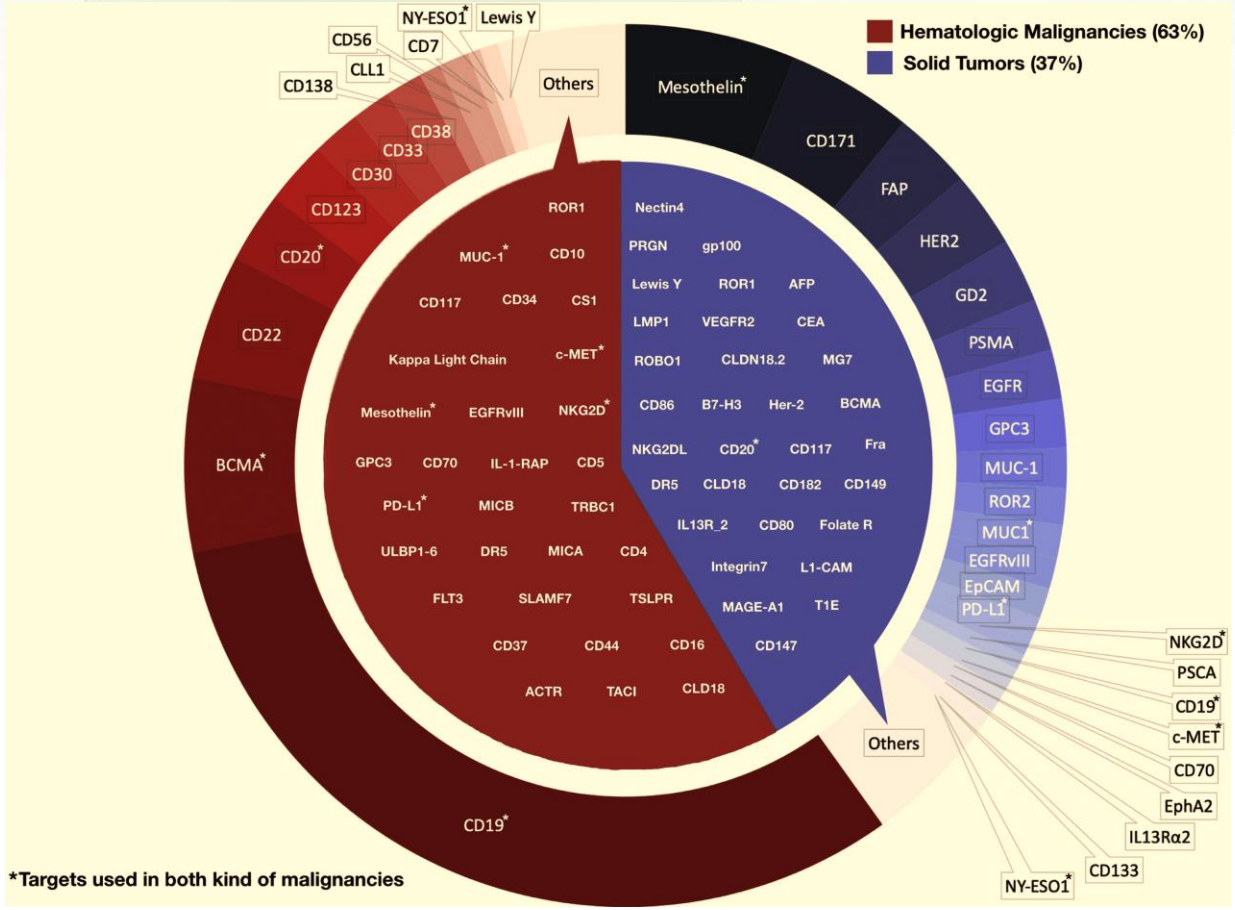
Trinn and Polyak. Cancer Cell. 2019

Terapias CAR-T en tumores sólidos : Antígenos diana

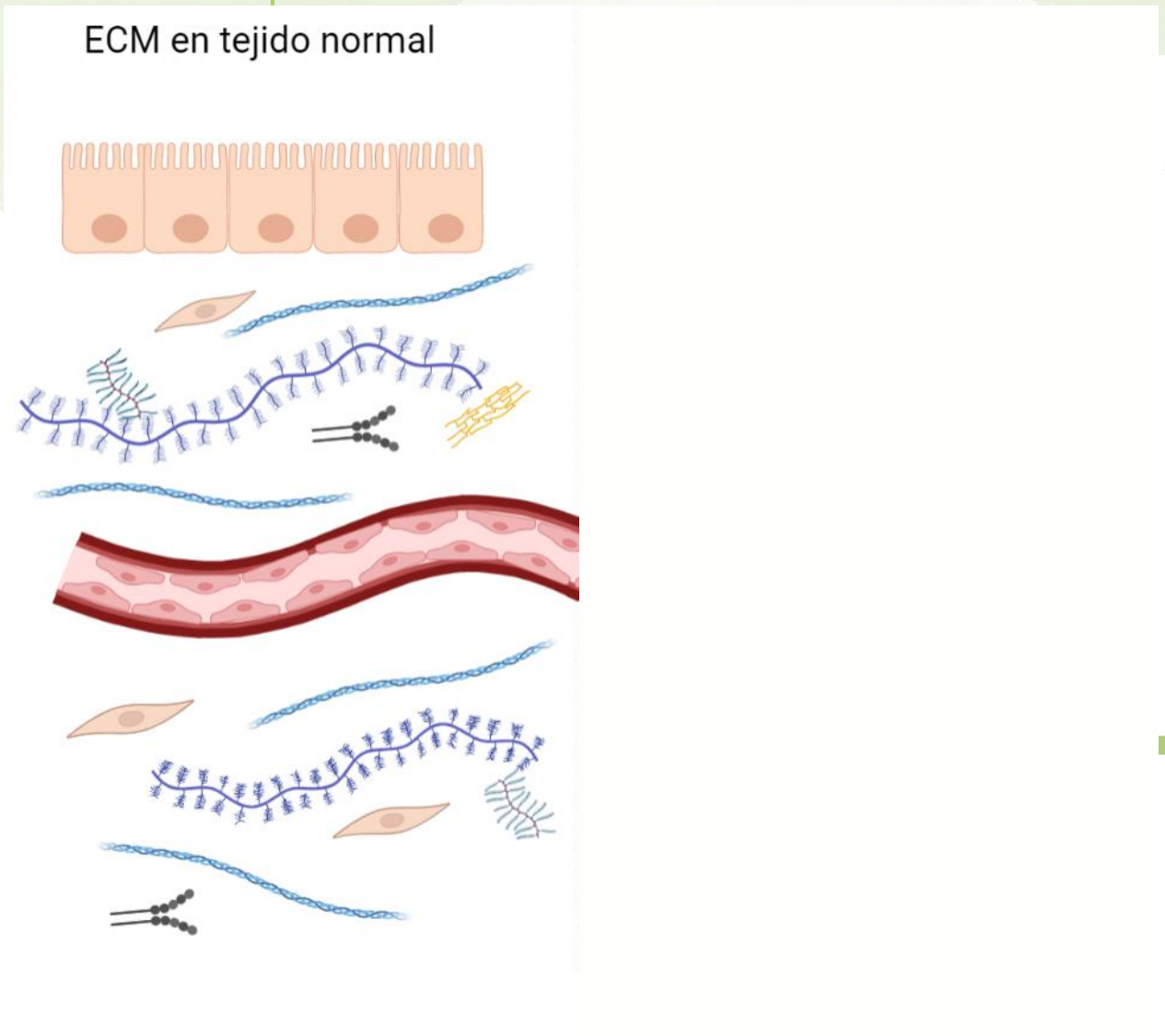




Target antigens used in CAR-T cell based therapies

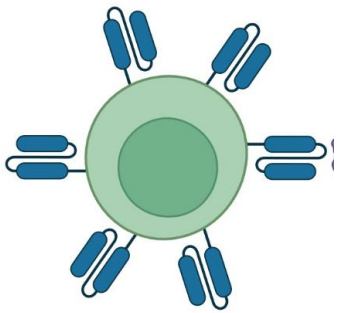


Microambiente tumoral: La Matriz extracelular como antígeno diana



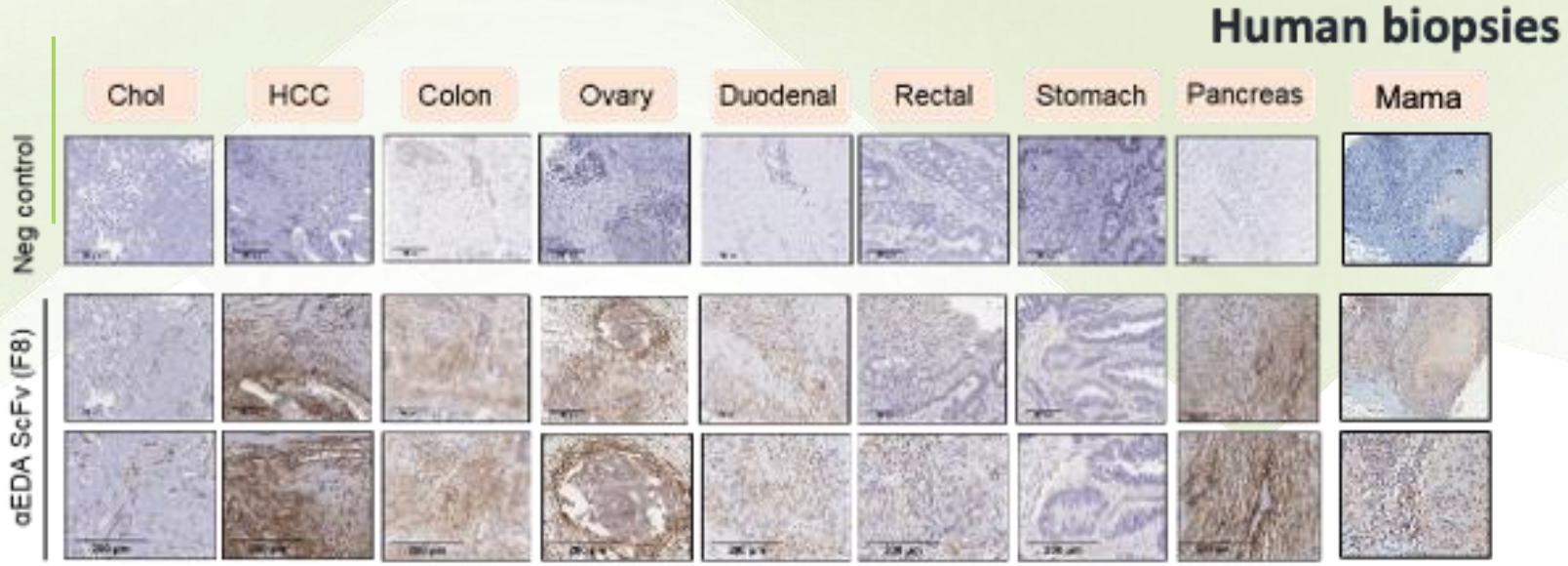
Dominio Extra A de la Fibronectina (EDA)

Anti EDA CART

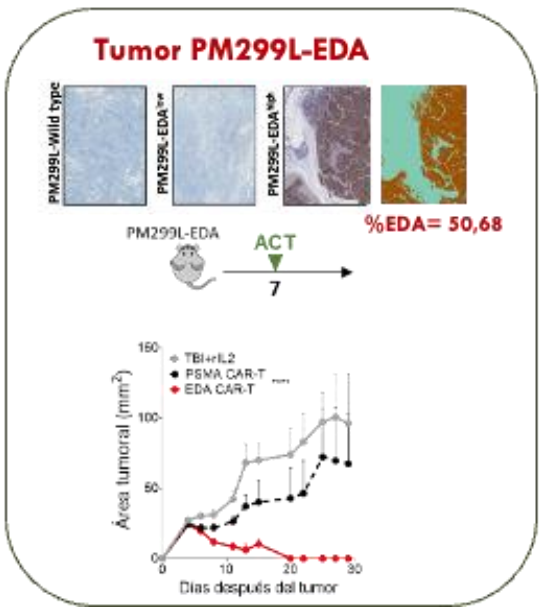


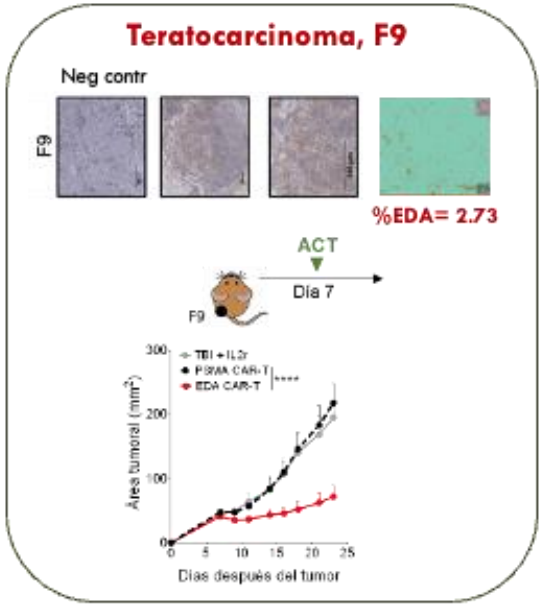
- Progresión tumoral
- Inmunosupresión
- Invasión y metástasis

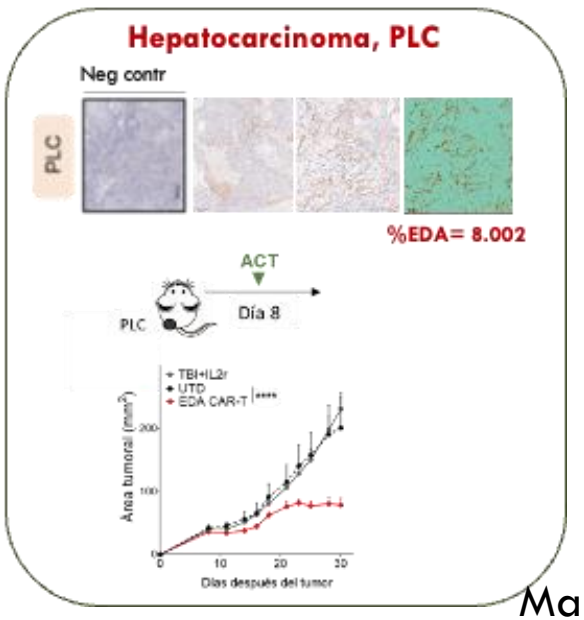
EDA CART para el tratamiento de tumores sólidos



Modelos donde EDA CART ha mostrado eficacia

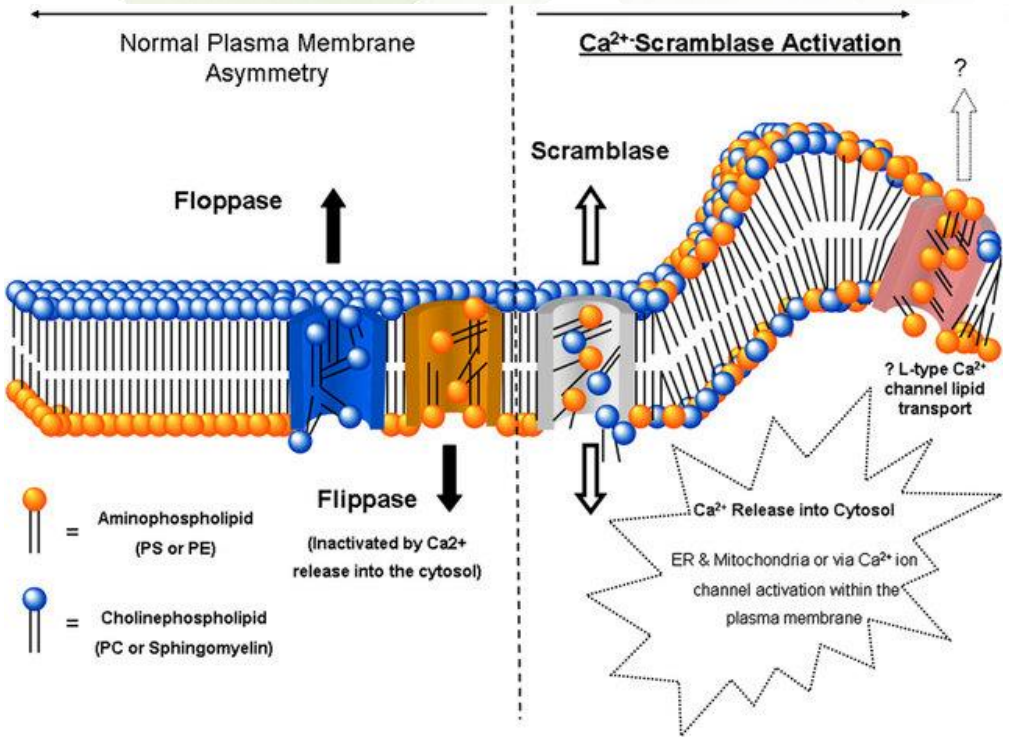


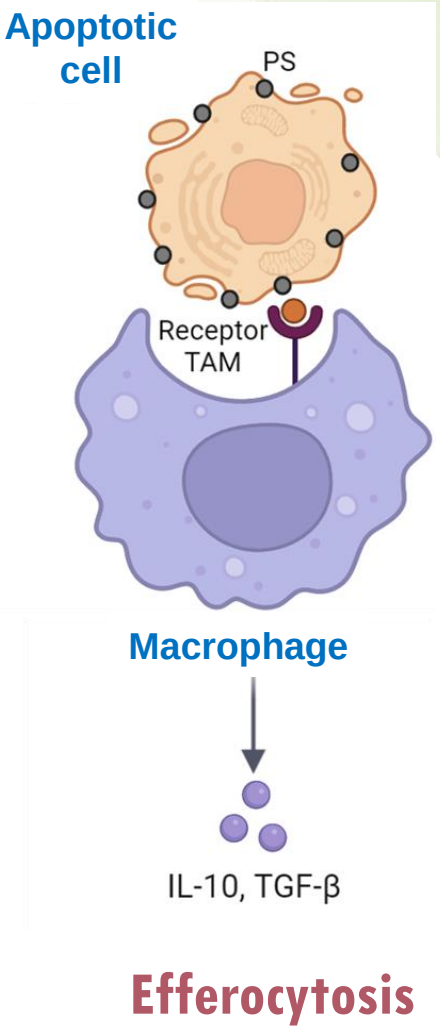


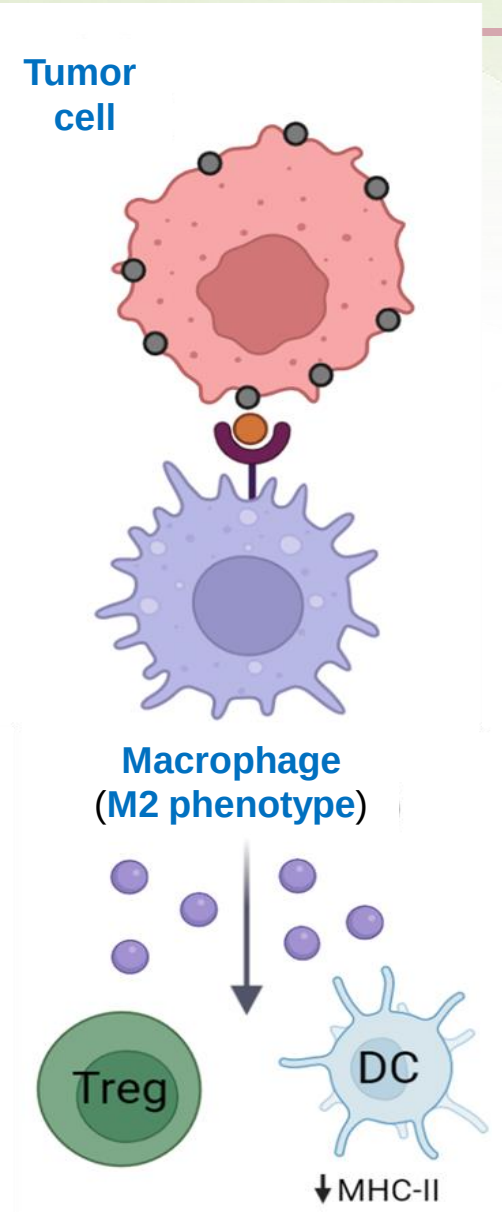


Martin-Otal et al, JITC, 2022

Papel de la exposición de PS en la homeostasis tisular



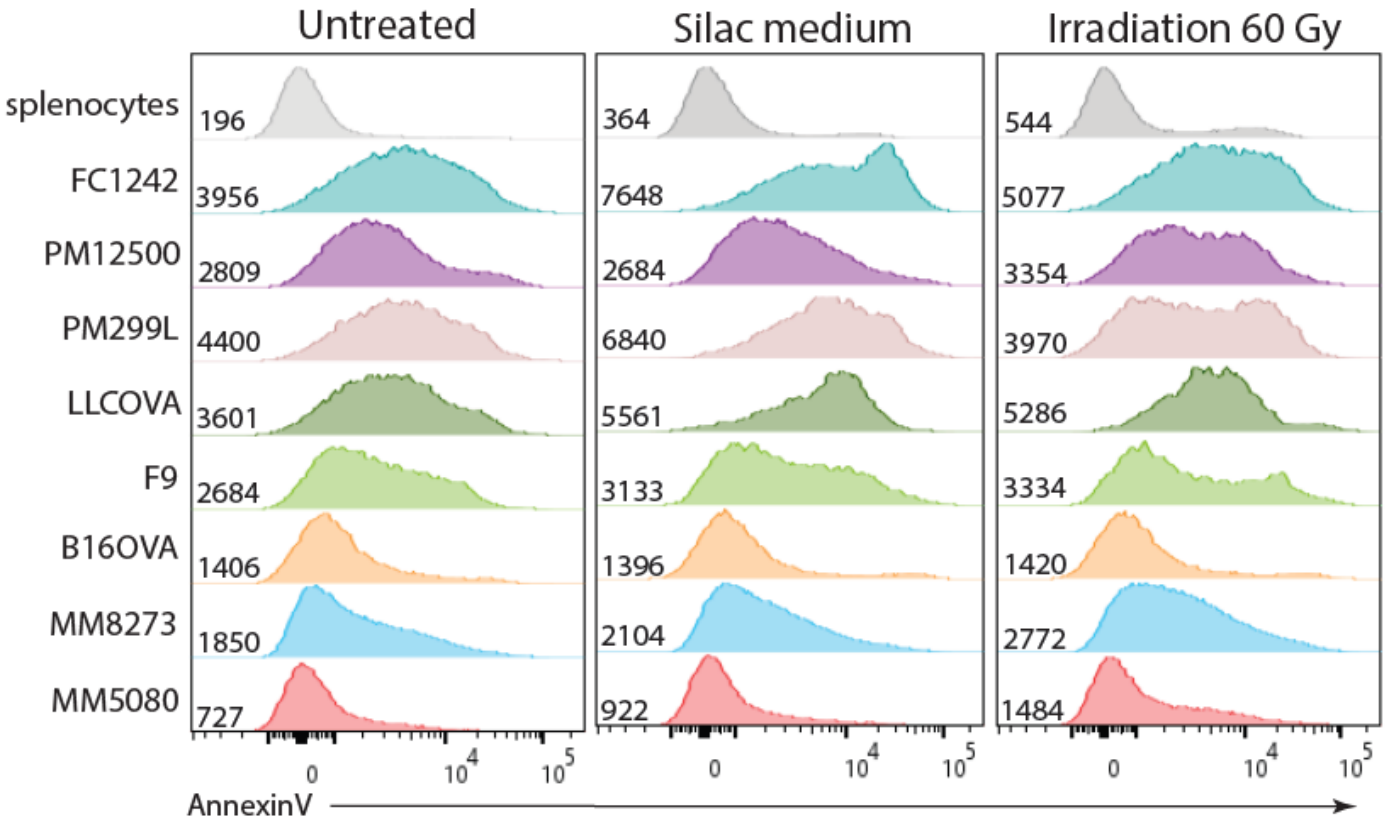




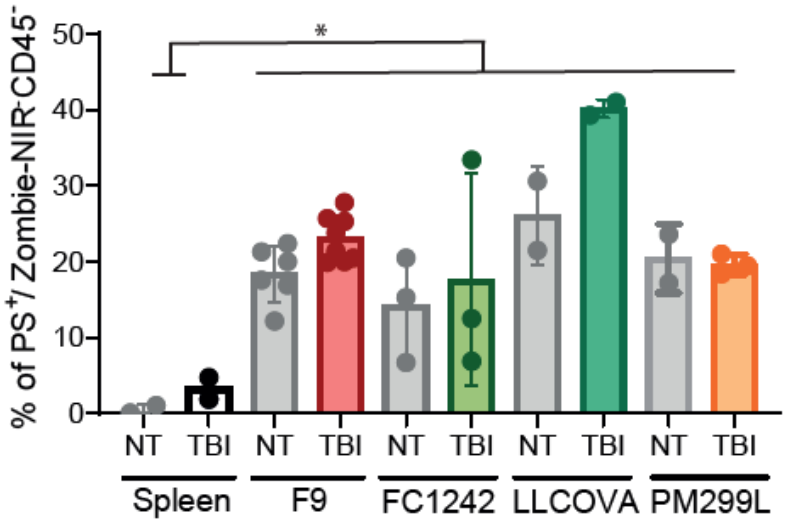
Lemke, G., et al. *Nat Rev Immunol (2008)*

PS se expone en líneas celulares tumorales y se une a la anexina V

Expresión PS en líneas celulares tumorales murinos



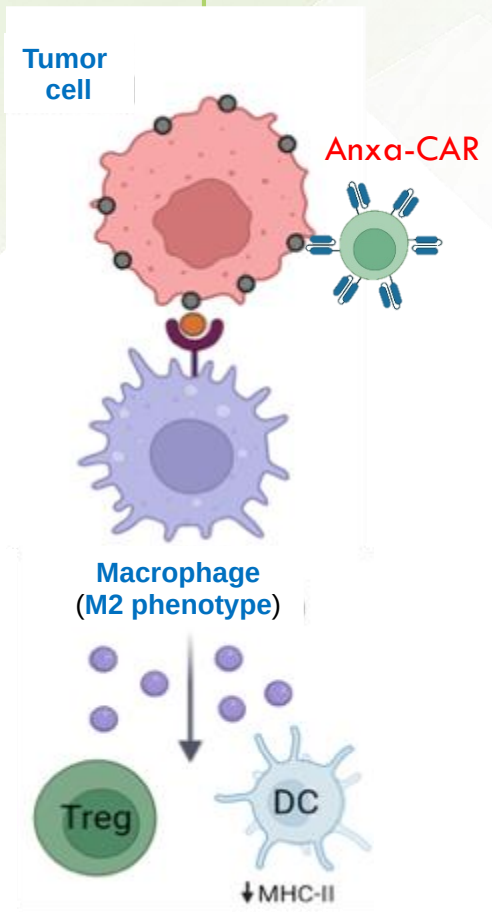
Expresión PS en tejidos tumorales murinos



Martin-Otal et al , JITC 2025

Búsqueda de antígenos: El estress de la célula tumoral como fuente de antígenos para inmunoterapia: La fosfatidilserina

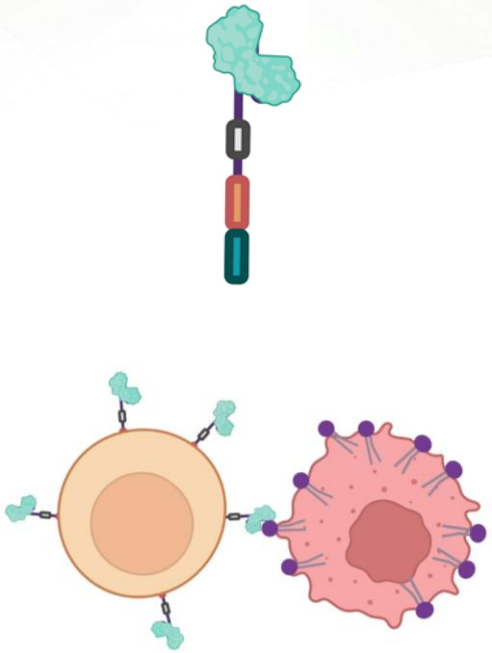
Mecanismo de escape tumoral



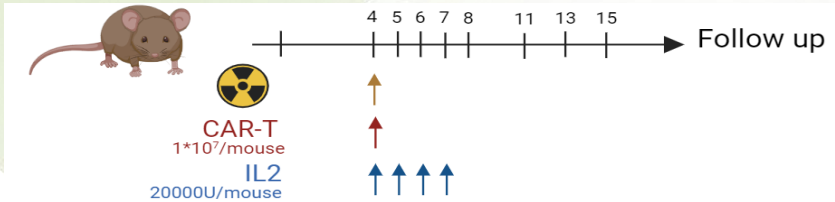
Immunosuppression

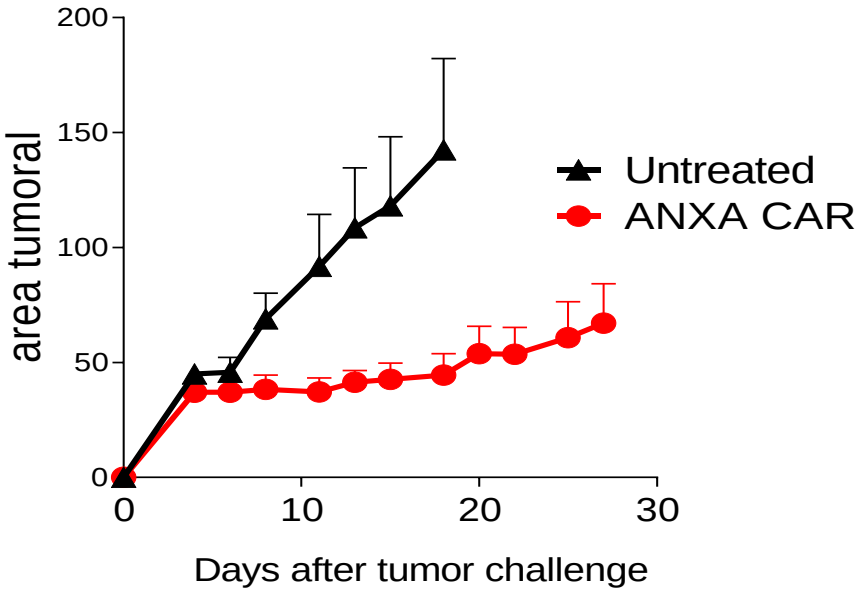
Blankenberg FG, Cancer Biol and Ther 2008

Anxa-CAR



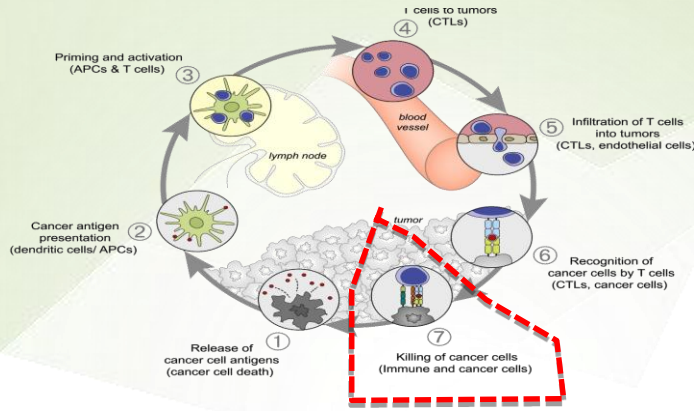
Modelo de hepatocarcinoma (PM299L)





Martin-Otal et al , JITC 2025

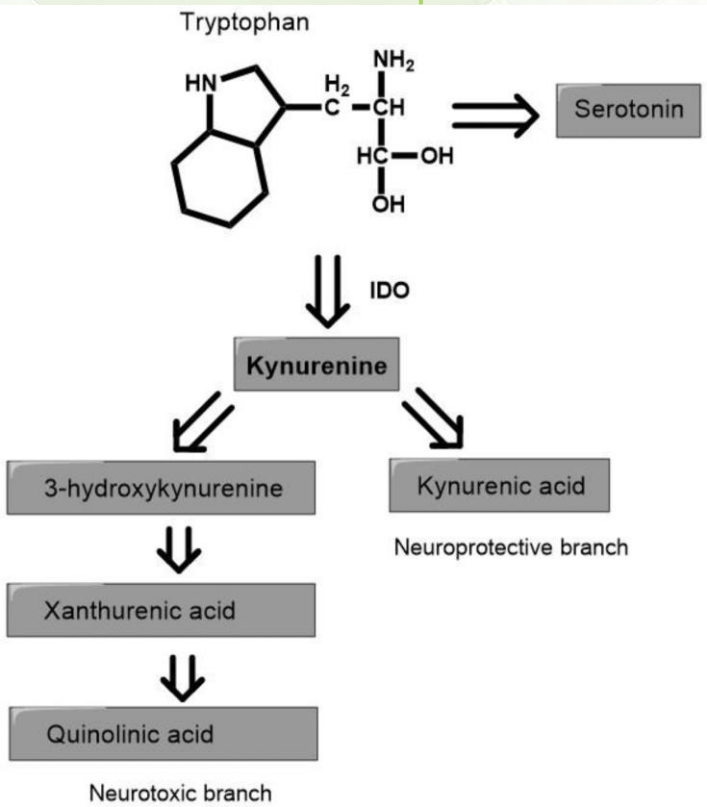
Reconocimiento y lisis de la célula tumoral

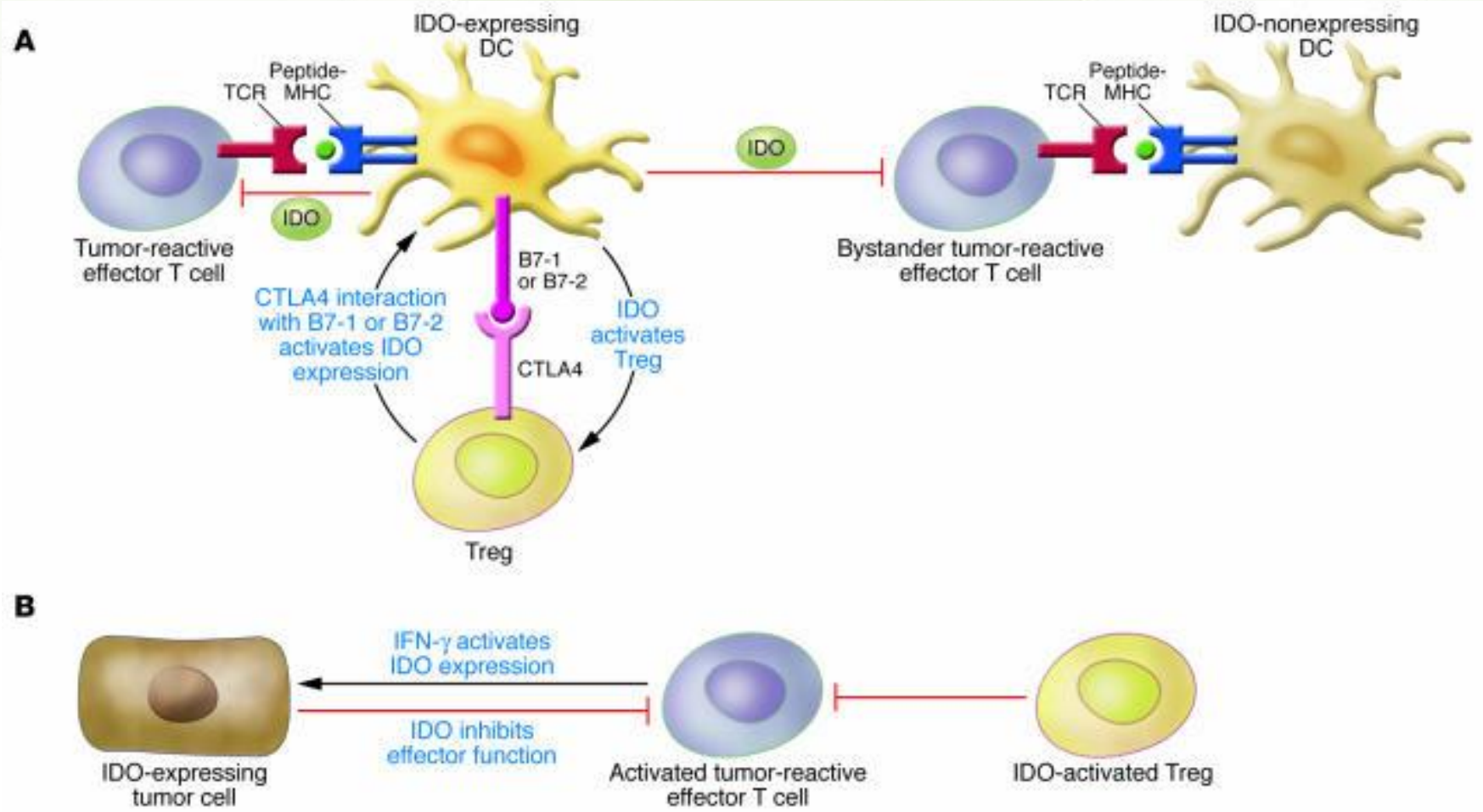


Factores que afectan al reconocimiento y lisis de la célula tumoral

- Proteínas inhibidoras (checkpoints) PD-1/PD-L1, LAG-3, BTLA, VISTA B7-H4, TIM-3, MICA/MICB
- Moléculas inmunosupresoras:
  - IDO
  - Arginasa
  - TGF-β

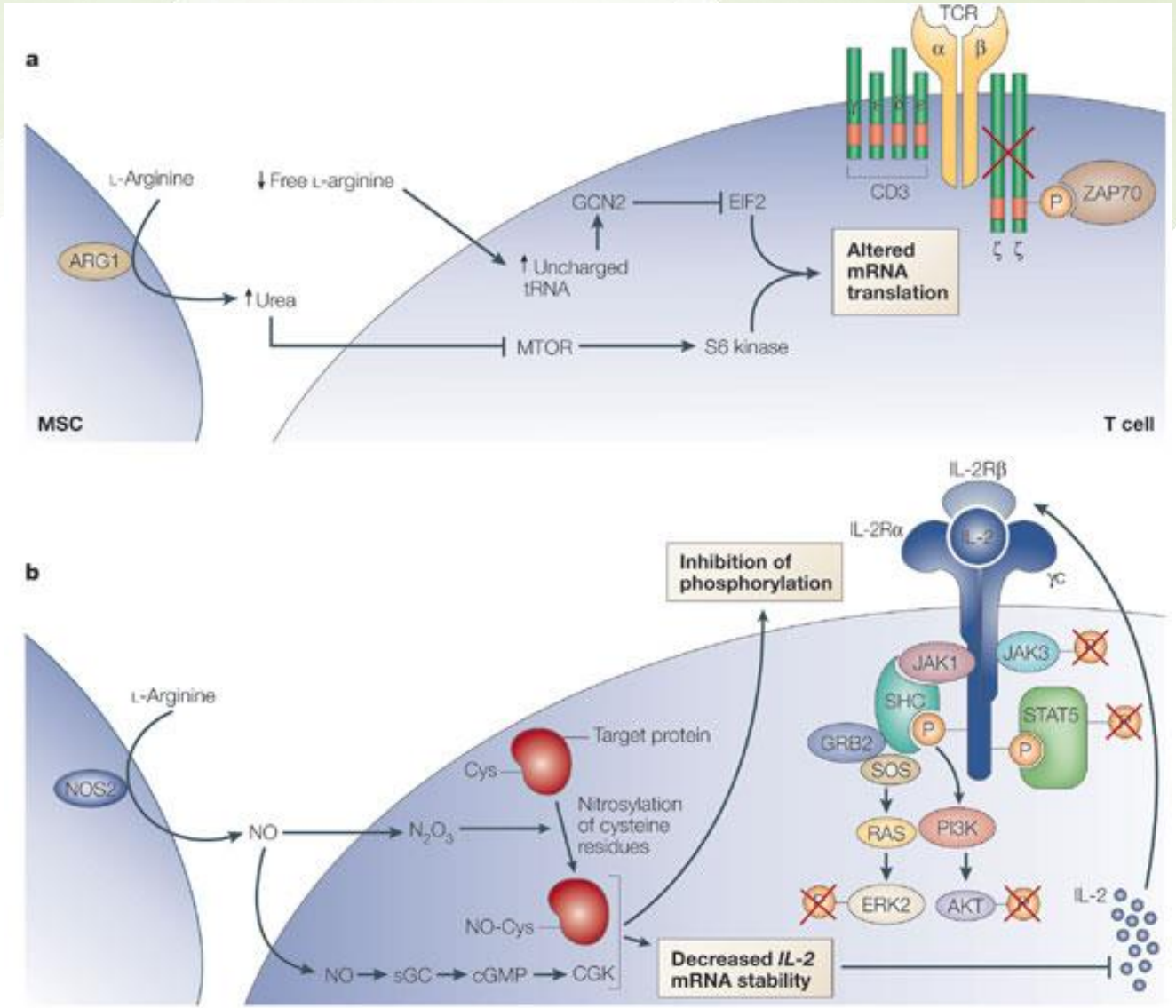
IDO y tolerancia inducida por los tumores





Mellor, Trends in Molecular Medicine 2004

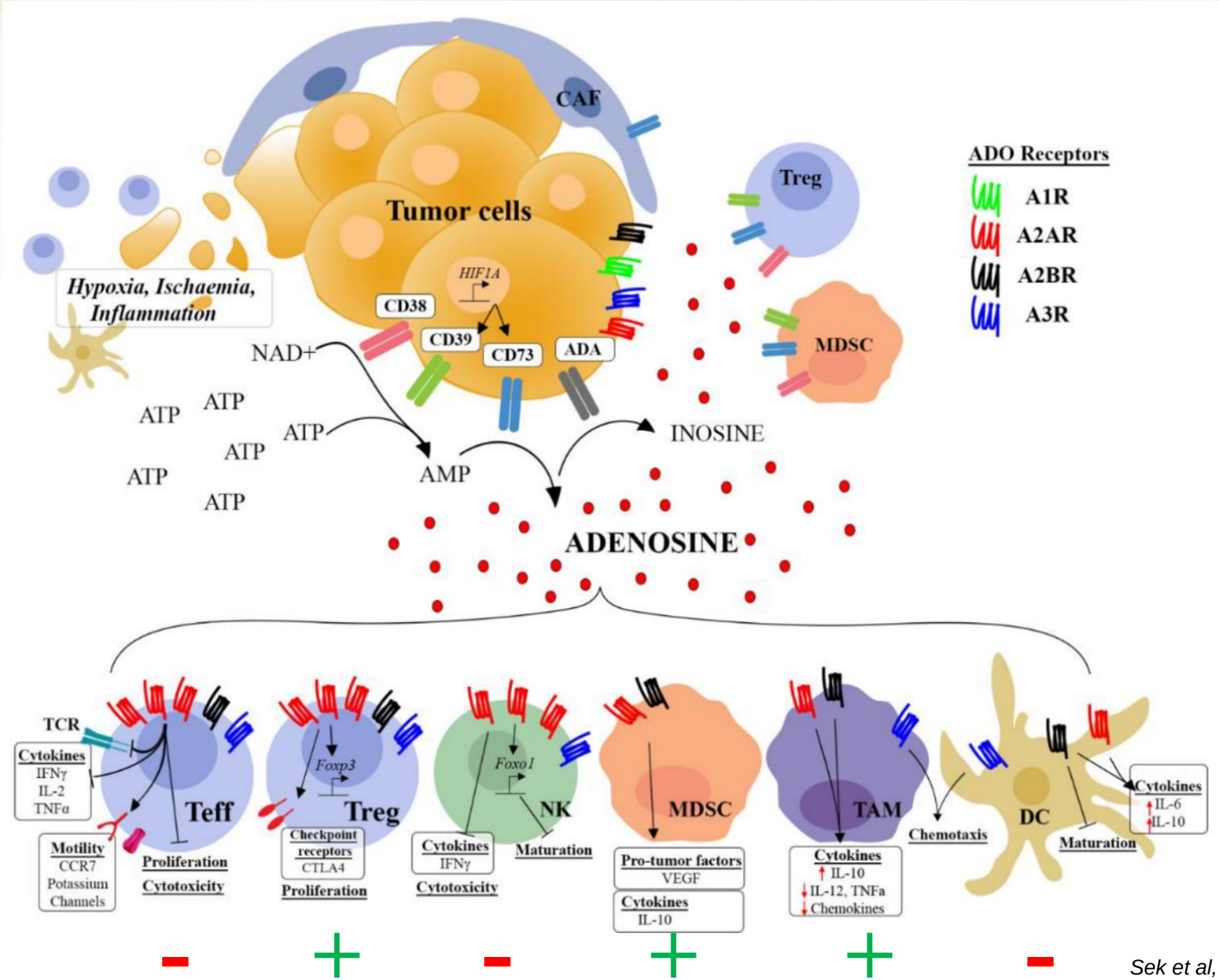
Control de la respuesta celular T por el metabolismo de la L-arginina



Bronte, Nat Rev Immunol, 2005

Metabolismo del ATP: generación de adenosina

Metabolismo del NAD+: generación de ADO



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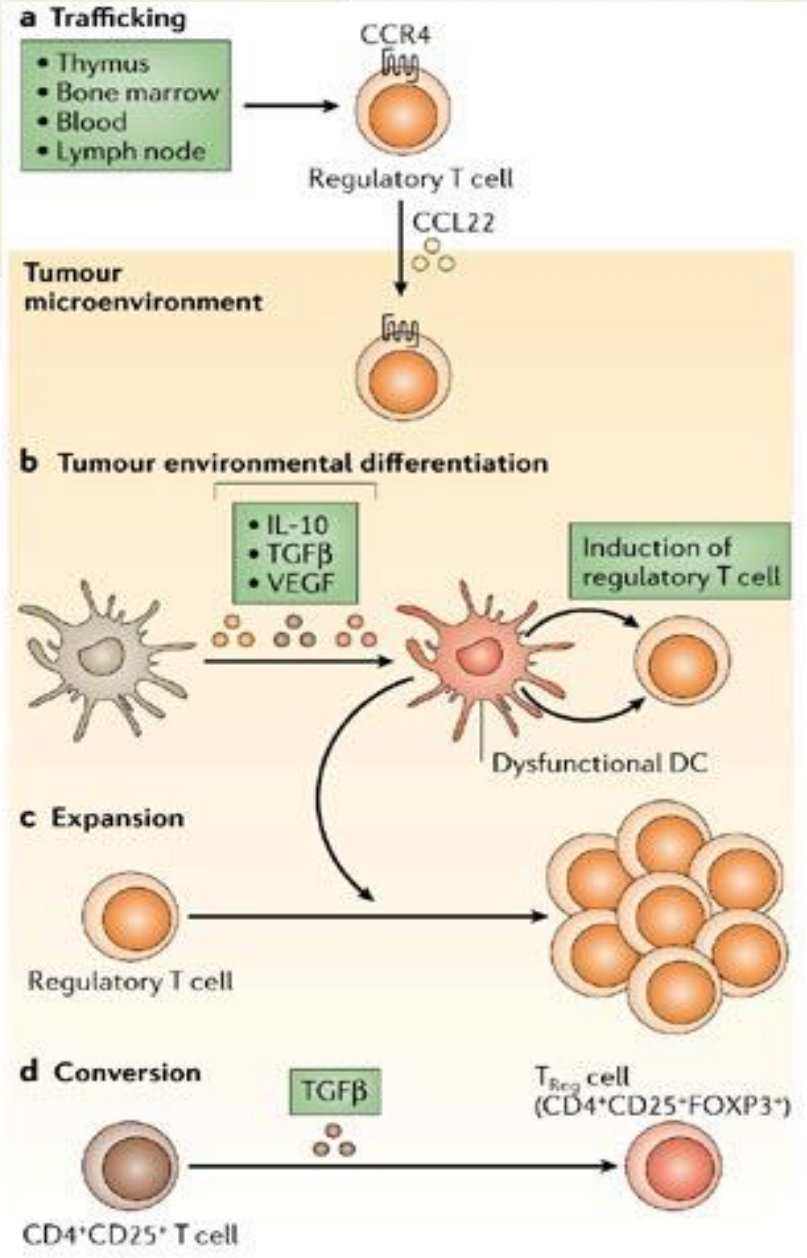
Linfocitos T reguladores (Treg) en los tumores



Fuentes potenciales de las células Treg que se encuentran en el tumor:

a | **Reclutamiento de Treg** provenientes del timo, bazo, nódulos linfáticos y sangre periférica . Las TReg cells expresan CCR4 (CCR4), y la producción de la quimiocina CCL22 (el ligando para CCR4) en el microambiente tumoral estimula el reclutamiento;

b | **Diferenciación.** El microambiente tumoral suprime a las APC convirtiendolas en APC tolerizantes que estimulan la diferenciaciónd elas Treg

c | **Expansion.** Las células dendríticas estimulan la expansión de las Treg

d | **Conversión.** Los linfocitos T efectores puedn convertirse en Treg a través de la acción del TGF-b que está sobreexpresado en el tumor.

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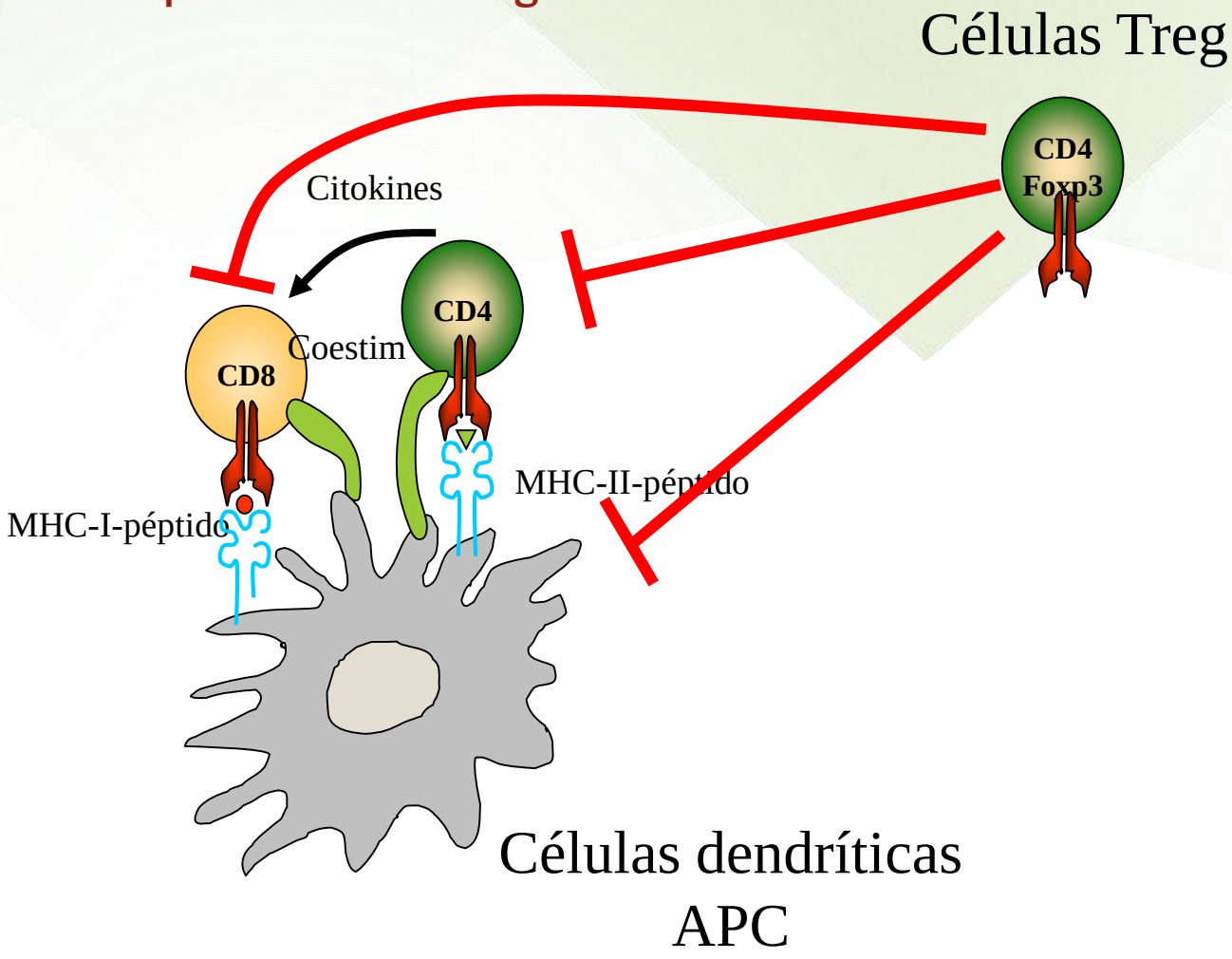
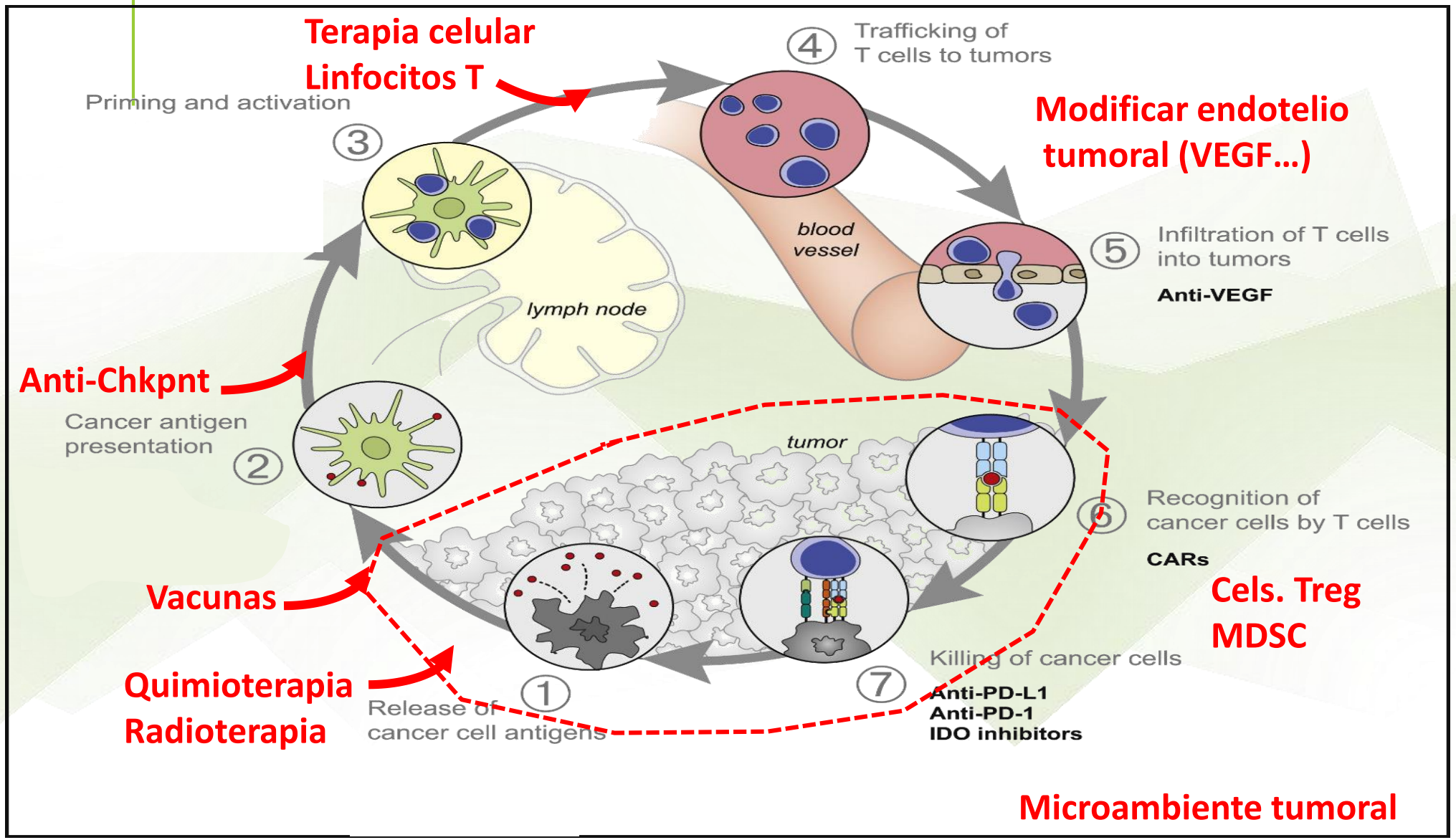
Zou, Nature Reviews Immunology, 2006

Inmunosupresión inducida por las células Treg



El ciclo "inmunidad-cancer". Estrategias terapéuticas



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LECTURAS OBLIGATORIAS

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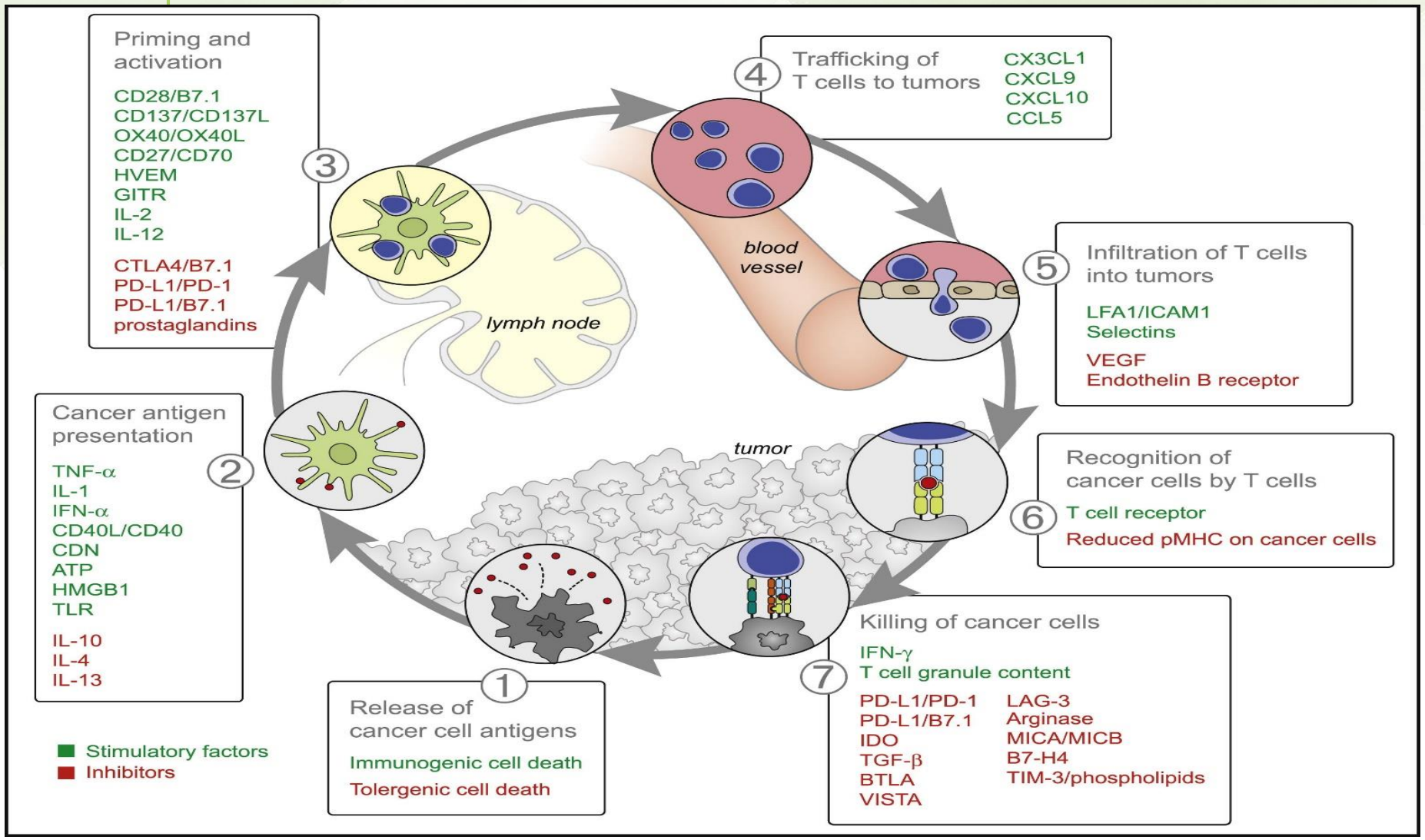
Impact of tumor microenvironment on adoptive T cell transfer activity. Martín-Otal C, Navarro F, Casares N, Lasarte-Cía A, Sánchez-Moreno I, Hervás-Stubbs S, Lozano T, Lasarte JJ.Int Rev Cell Mol Biol. 2022;370:1-31. doi: 10.1016/bs.ircmb.2022.03.002. Epub 2022 Jun 21

El ciclo "inmunidad-cancer". Estrategias terapéuticas

Factores estimuladores e inhibidores



Chen and Mellman. Immunity. 2013