VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 20 y 21 de febrero de 2025

Inmunomodulación y microambiente tumoral

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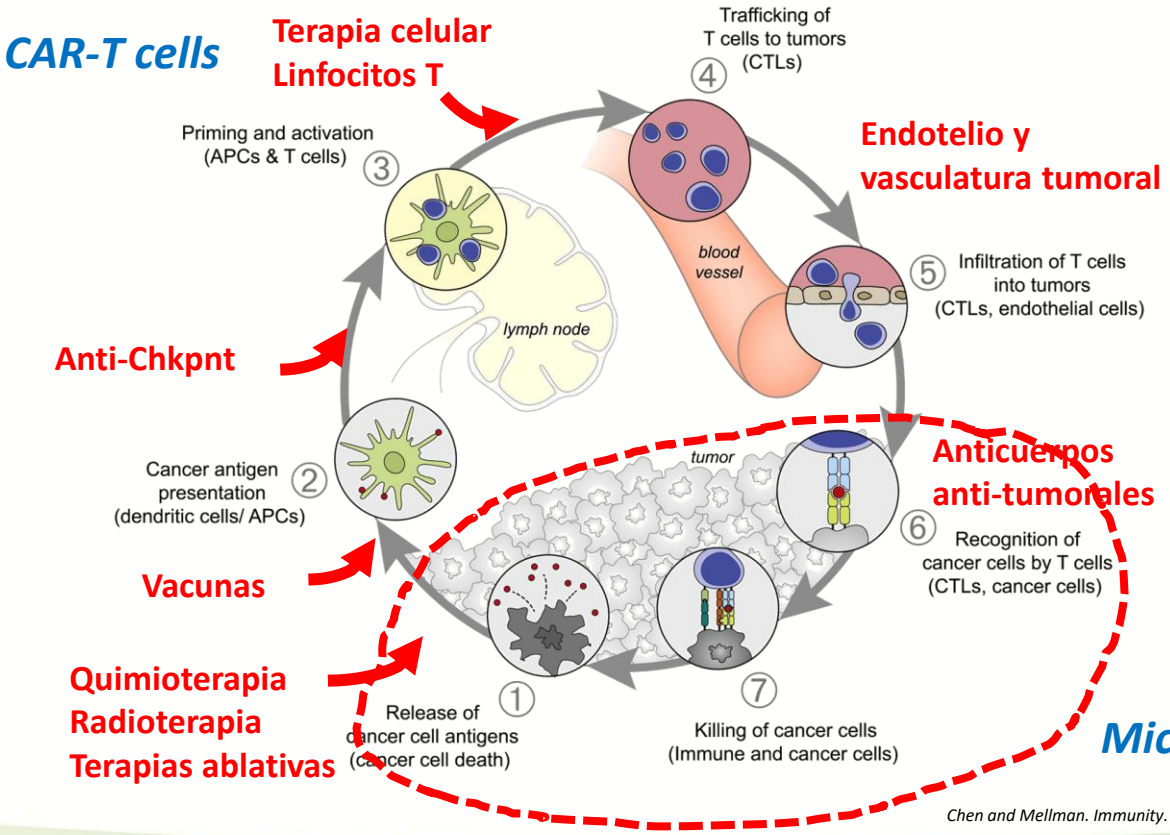
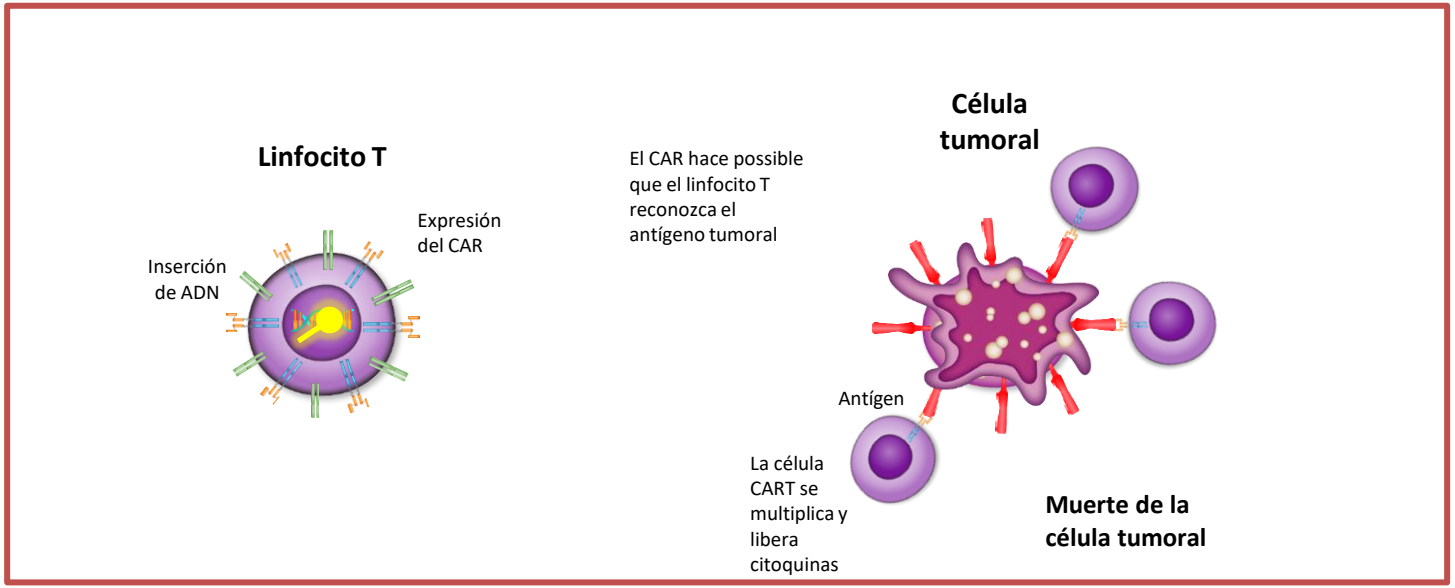
Pamplona

Mecanismos de evasión tumoral
El ciclo "inmunidad-cancer"

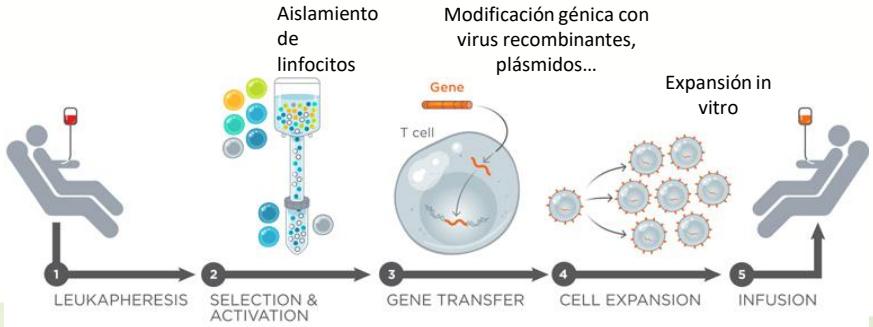


Chen and Mellman. Immunity. 2013

CAR T cells: Mecanismo de acción

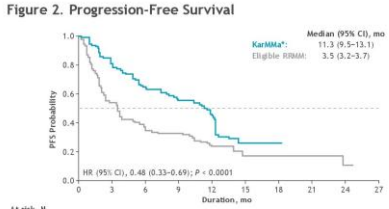


Manufactura de los CAR-T cells



- ALL: 90% eficacia (Ag: CD19)
- Linfoma: 50% eficacia, (Ag: CD19)
- MM, 70-80% eficacia (Ag: BCMA)

CAR-antiBCMA
PFS:(Karmma)



Éxitos de los CART en tumores sólidos

nature medicine

Brief Communication

https://doi.org/10.1038/s41591-025-03513-0

Long-term outcomes of GD2-directed CAR-T cell therapy in patients with neuroblastoma

Received: 7 April 2024

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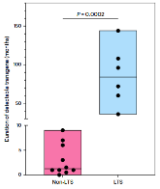
Che-Hsing Li[1,2,3], Sandhya Sharma[1], Andras A. Heczey[1,2,4], Mae L. Woods[1], David H. M. Steffin[1,4], Chrystal U. Louis[1], Bambi J. Grilley[1,4], Sachin G. Thakkar[1], Mengfen Wu[4], Tao Wang[4], Cliona M. Rooney[1,4], Malcolm K. Brenner[1,4] & Helen E. Heslop[1,4]

Despite using first-generation vectors that are no longer employed because of the lack of co-stimulatory domains, patients with relapsed/refractory neuroblastoma achieved long-term disease control after receiving GD2 CAR-T cell therapy, including one patient now in remission of relapsed disease for more than 18 years. ClinicalTrials.gov identifier: NCT00085930.



Article

Intravenous and intracranial GD2-CAR T cells for H3K27M$^+$ diffuse midline gliomas

https://doi.org/10.1038/s41586-024-08171-9

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Open access

Check for updates

Michelle Monje[1,2,3,4,5,6], Jasia Mahdi[1,3], Robbie Majzner[2,3], Kristen W. Yeom[1,4,7], Liora M. Schultz[2,3], Rebecca M. Richards[2,3], Valentin Barsan[2,3], Kun-Wei Song[1,3], Jen Kamens[2,3], Christina Baggott[3], Michael Kunicki[3], Skyler P. Rietberg[3], Alexandria Sung Lim[3], Agnes Reschke[2,3], Sharon Mavroukakis[3], Emily Egeler[3], Jennifer Moon[3], Shabnum Patel[3], Harshini Chinnasamy[3], Courtney Erickson[3], Ashley Jacobs[3], Allison K. Duh[4], Ramya Tunuguntla[3], Dorota Danuta Klysz[3], Carley Fowler[3], Sean Green[3], Barbara Beebe[3], Casey Carr[3], Michelle Fujimoto[3], Annie Kathleen Brown[3], Ann-Louise G. Petersen[3], Catherine McIntyre[8], Aman Siddiqui[8], Nadia Lepori-Bui[8], Katlin Villar[8], Kymhuynh Pham[8], Rachel Bove[8], Eric Musa[8], Warren D. Reynolds[3], Adam Kuo[3], Snehit Prabhu[3], Lindsey Rasmussen[9], Timothy T. Cornell[9], Sonia Partap[1], Paul G. Fisher[1], Cynthia J. Campen[1], Gerald Grant[4], Laura Prolo[4], Xiaobu Ye[10], Bita Sahaf[3], Kara L. Davis[2,3], Steven A. Feldman[3], Sneha Ramakrishna[2,3] & Crystal Mackall[2,3,11,12]

Nine patients received ICV infusions, with no dose-limiting toxicities. All patients exhibited tumour inflammation-associated neurotoxicity, safely managed with intensive monitoring and care. Four patients demonstrated major volumetric tumour reductions (52, 54, 91 and 100%), with a further three patients exhibiting smaller reductions. One patient exhibited a complete response ongoing for over 30 months since enrolment. Nine patients demonstrated neurological benefit,

VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

Pobre eficacia de los CART en tumores sólidos

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

Bryan D. Choi, M.D., Ph.D., Elizabeth R. Gerstner, M.D., Matthew J. Frigault, M.D., Mark B. Leick, M.D., Christopher W. Mount, M.D., Ph.D., Leonora Balaj, Ph.D., Sarah Nikiforow, M.D., Ph.D., Bob S. Carter, M.D., Ph.D., William T. Curry, M.D., Kathleen Gallagher, Ph.D., and Marcela V. Maus, M.D., Ph.D.

nature cancer

Article

https://doi.org/10.1038/s43018-023-00709-6

Repeated peripheral infusions of anti-EGFRvIII CAR T cells in combination with pembrolizumab show no efficacy in glioblastoma: a phase 1 trial

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Stephen J. Bagley[1,25], Zev A. Binder[2,3,4,25], Lamia Lamrani[5,6,7,25], Eliana Marinari[8,9,10,11], Arati S. Desai[1], MacLean P. Nasrallah[4,12], Eileen Maloney[2], Steven Brem[2,4], Robert A. Lustig[13], Goldie Kurtz[13], Michelle Alonso-Basanta[13], Pierre-Emmanuel Bonté[6], Christel Goudot[6], Wilfrid Richer[6,14], Eliane Piaggio[6], Shawn Kothari[15], Lea Guyonnet[16], Coralie L. Guerin[16], Joshua J. Waterfall[14,17], Suyash Mohan[18], Wei-Ting Hwang[19], Oliver Y. Tang[4,20], Meghan Logun[2,3,4], Meghna Bhattacharyya[4,21], Kelly Markowitz[1], Devora Delman[1], Amy Marshall[3], E. John Wherry[7,22,23], Sebastian Amigorena[6], Gregory L. Beatty[1,4], Jennifer L. Brogdon[24], Elizabeth Hexner[1], Denis Migliorini[8,9,10,11], Cecile Alanio[5,6,7] & Donald M. O'Rourke[2,3,4]

Open access Original research

Journal for ImmunoTherapy of Cancer

Safety and biological outcomes following a phase 1 trial of GD2-specific CAR-T cells in patients with GD2-positive metastatic melanoma and other solid cancers

Tessa Gargett,[1,2,3] Nga T H Truong,[1,3] Bryan Gardam,[1,2] Wenbo Yu,[1,3] Lisa M Ebert,[1,2,3] Amy Johnson,[4] Erica C F Yeo,[1] Nicole L Wittwer,[1,3] Gonzalo Tapia Rico,[2,3] Jesikah Logan,[3] Purany Sivaloganathan,[3] Maria Collis,[5] Andrew Ruszkiewicz,[2,5,6] Michael P Brown[1,2,3]

nature medicine

Article

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PSCA-CAR T cell therapy in metastatic castration-resistant prostate cancer: a phase 1 trial

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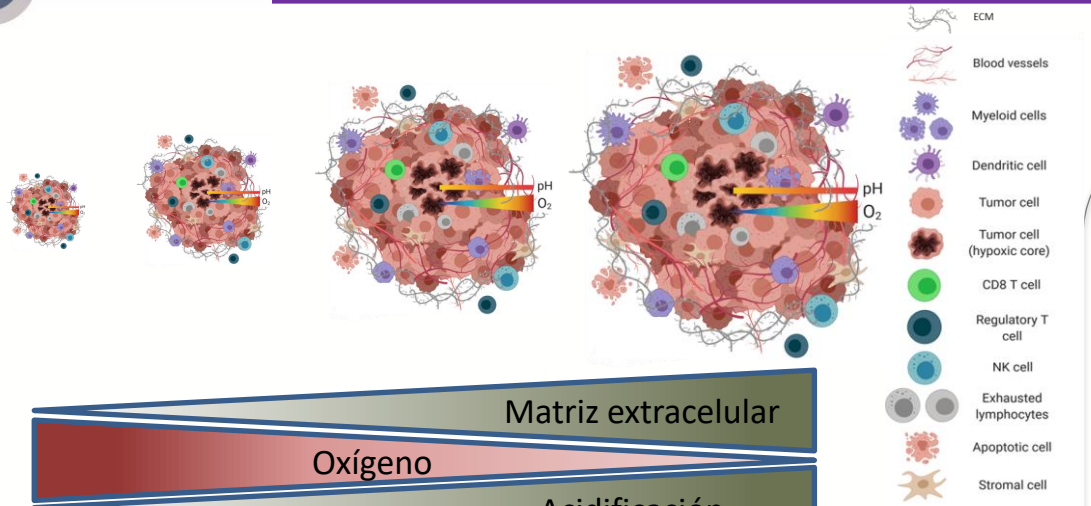
Tanya B. Dorff[1], M. Suzette Blanchard[2], Lauren N. Adkins[3], Laura Luebbert[4], Neena Leggett[3], Stephanie N. Shishido[5], Alan Macias[3], Marissa M. Del Real[3], Gaurav Dhapola[3], Colt Egelston[6], John P. Murad[3], Reginaldo Rosa[3], Jinny Paul[3], Ammar Chaudhry[7], Hripsime Martirosyan[1], Ethan Gerdts[3], Jamie R. Wagner[3], Tracey Stiller[2], Dileshni Tilakawardane[3], Sumanta Pal[1], Catalina Martinez[8], Robert E. Reiter[9], Lihua E. Budde[3], Massimo D'Apuzzo[10], Peter Kuhn[5], Lior Pachter[4], Stephen J. Forman[3,6] & Saul J. Priceman[3,6]

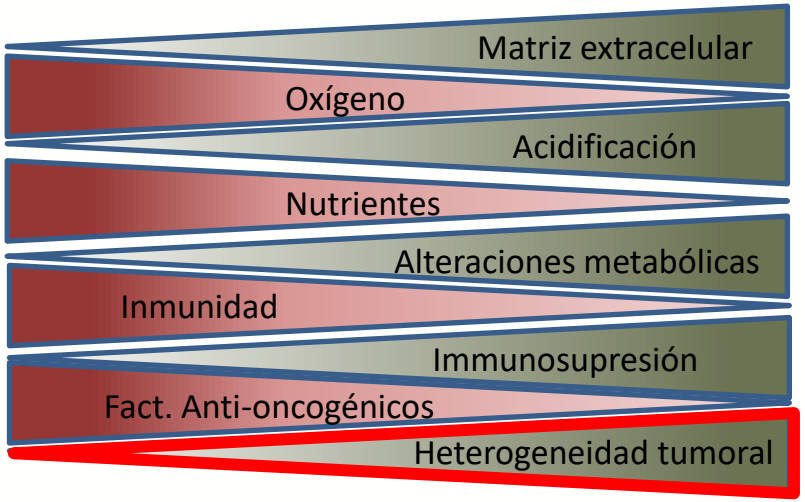
Original Reports | Pediatric Oncology

STRIvE-02: A First-in-Human Phase I Study of Systemically Administered B7-H3 Chimeric Antigen Receptor T Cells for Patients With Relapsed/Refractory Solid Tumors

Navin Pinto, MD[1,2]; Catherine M. Albert, MD[1,2]; Mallory R. Taylor, MD[1,2]; Heidi B. Ullom, RN, BSN, CPON[1]; Ashley L. Wilson, PhD[3]; Wenjun Huang, PhD[3]; Jason Wendler, PhD[3]; Sowmya Pattabhi, PhD[3]; Kristy Seidel, MS[3]; Christopher Brown, BA[3]; Joshua A. Gustafson, PhD[3]; Stephanie D. Rawlings-Rhea, BS[3]; Safia H.E. Cheeney, MD[4]; Katelyn Burleigh, PhD[2]; Heather H. Gustafson, PhD[2]; Rimas J. Orentas, PhD[1,2]; Nicholas A. Vitanza, MD[1,2]; Rebecca A. Gardner, MD[1,2]; Michael C. Jensen, MD[3]; and Julie R. Park, MD[1,2]

Dinámica del microambiente tumoral





Dificultades

- Falta de antígenos específicos en tumores sólidos?

1. Barrearas físicas que dificultan el tráfico linfocitario

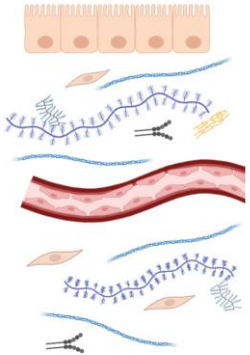
- Vasculatura tumoral aberrante

- Señales y ambiente inmunosupresores del TME:
  - pH acídico,
  - Deprivación de nutrientes,
  - Células inmunosurpresoras (Treg cells…)
  - Citoquinas inmunosupresoras
  - …

2.

La matriz extracellular tumoral: Una Fuente de antígenos para la inmunoterapia

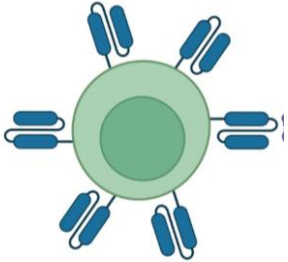
ECM in normal tissues



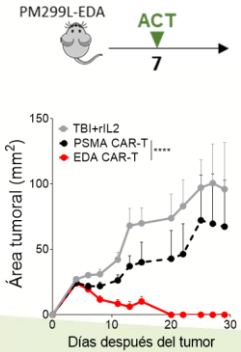
Hialuronan
Proteoglycan
Elastin
Collagen
Fibronectin → Extra domain A from fibronectin (EDA)
Fibroblast
Activated Fibroblast

→ Tumor progression
Inmunosupression
Invasion and metastasis

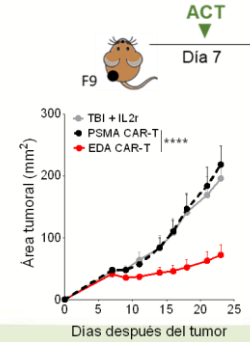
Anti EDA CART



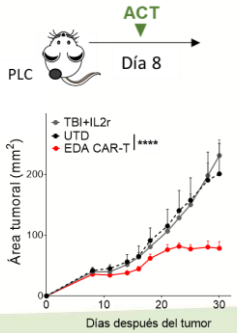
Tumor PM299L-EDA establecido



Tumor de teratocarcinoma F9
(EDA en endotelio de nueva formación)



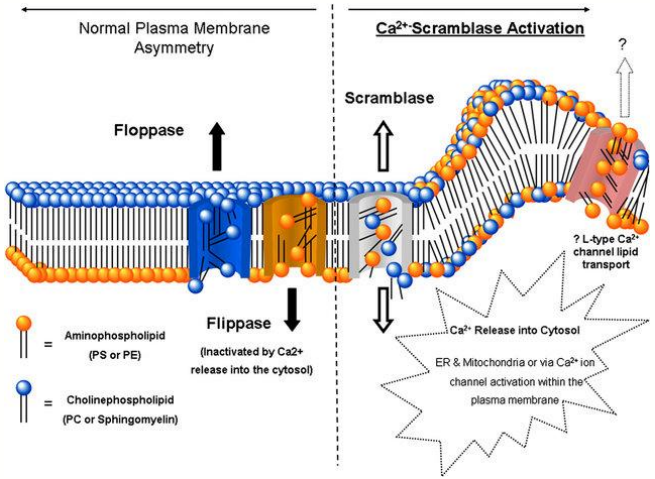
Modelo de hepatocarcinoma PLC
(EDA asociada a ECM y endotelio)



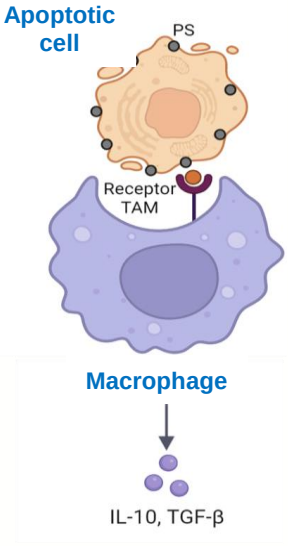
Martín-Otal et al, 2023

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

Asimetría de la membrana celular:
regulada por flipasa, flopasa and scramblasa

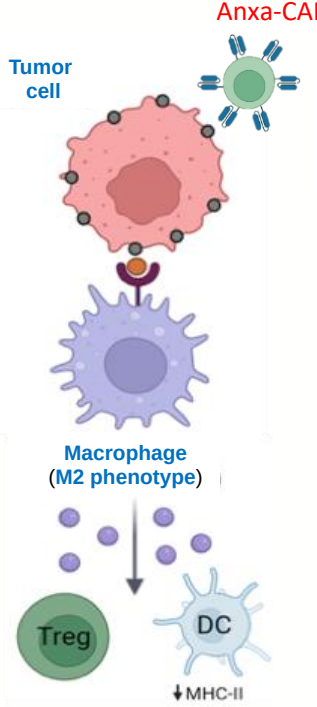


Blankenberg FG, Cancer Biol and Ther 2008



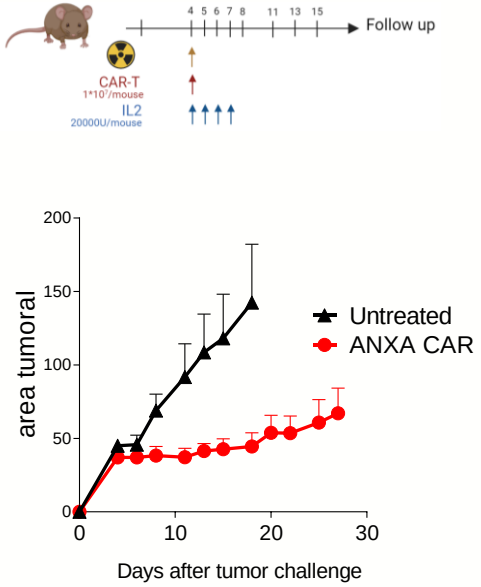
Efferocytosis

Mecanismo de escape tumoral



Immunosuppression

Modelo de hepatocarcinoma (PM299L)



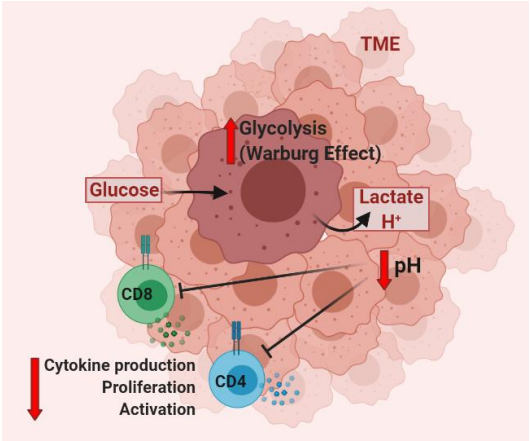
Martin-Otal, JITC 2025, in press

El microambiente tumoral afecta a la eficacia de las terapias de células T adoptivas

El microambiente tumoral acídico (TME) inhibe la funcionalidad de los linfocitos

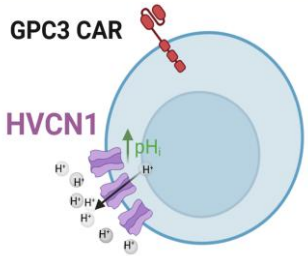
Dificultad

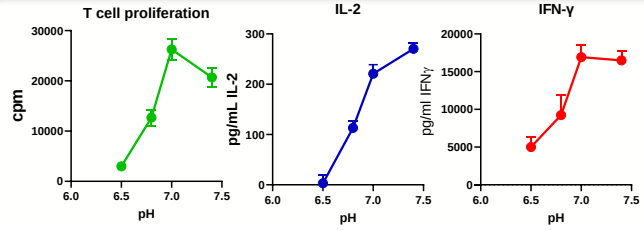
- pH acídico del microambiente tumoral



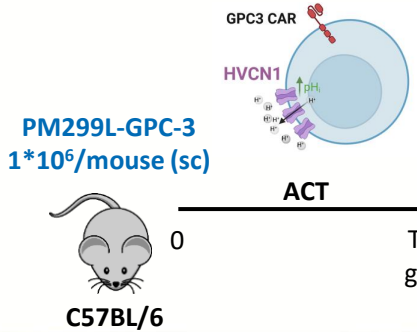
Qué podemos hacer para que los linfocitos T resistan el pH acídico del tumor?

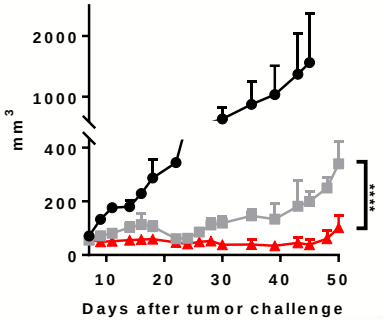
- El alto ritmo glicolítico de las células tumorales resulta en la acidificación del pH del microambiente tumoral
- El pH acídico inhibe la activación de las células T, su proliferación y la respuesta inmunitaria antitumoral





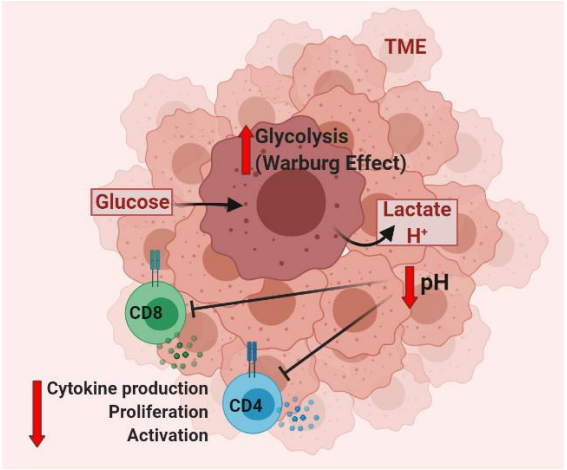
OT-1 T cells stimulated with SIINFEKL peptide at different pH



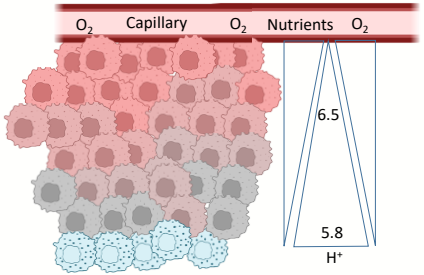


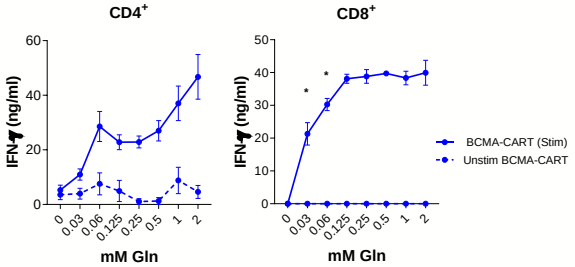
El microambiente tumoral afecta a la eficacia de las terapias de células T adoptivas

La deprivación de nutrientes en el TME inhibe la función de los linfocitos: La **Glutamina**

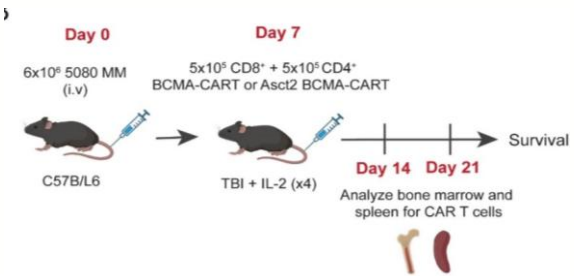


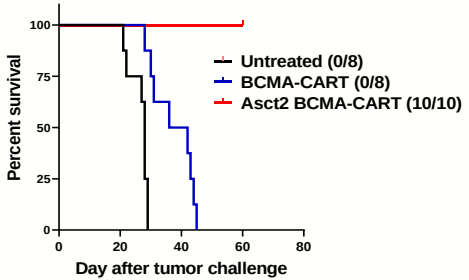
- Muchos tumores, especialmente el mieloma múltiple, dependen de la glutamina para su crecimiento y supervivencia.
- Hay una deprivación de glutamina en el microambiente tumoral
- Los linfocitos T antitumorales dependen fuertemente de la disponibilidad de glutamina.





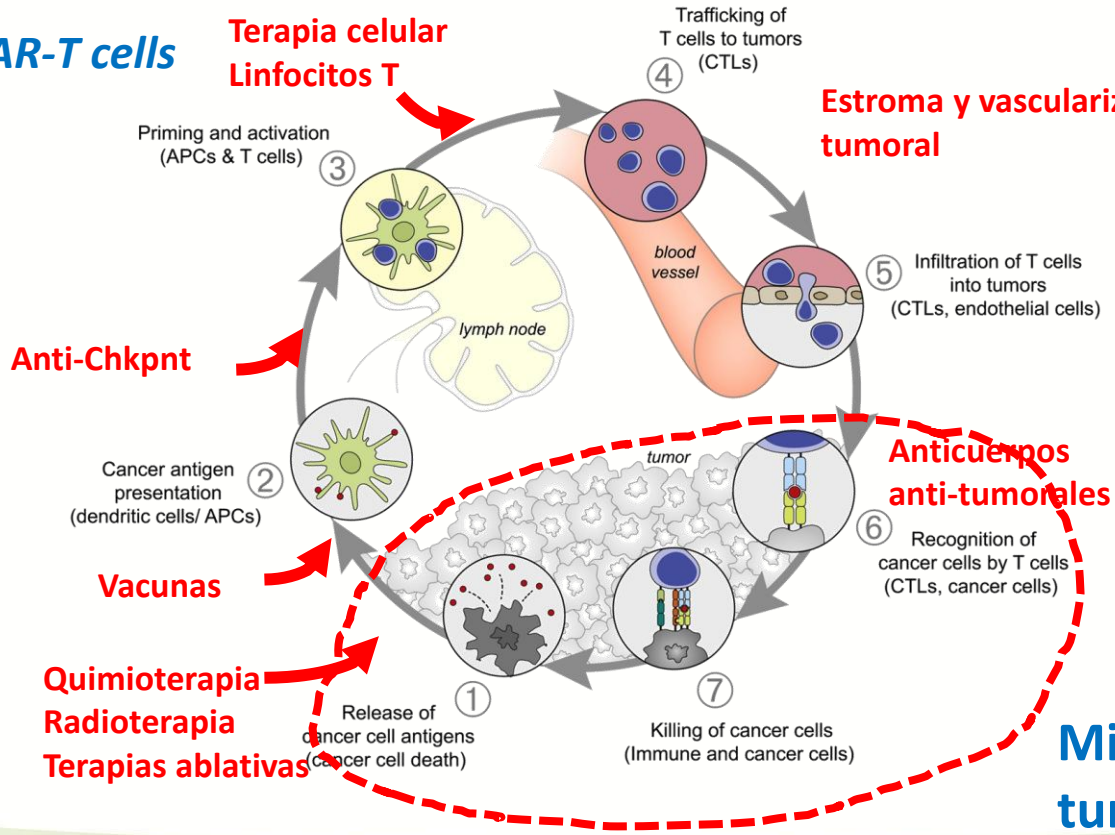
Qué podemos hacer para que los linfocitos funcionen en un ambiente pobre en glutamina?





Navarro et al, under review

Mecanismos de evasión tumoral
El ciclo "inmunidad-cancer"



Chen and Mellman. Immunity. 2013

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