ÁREA: CÁNCER

Grupo: Hematología Experimental
(Inmunoterapia celular)

Inmunoterapia con células CAR-T: limitaciones y estrategias para mejorar la persistencia y eficacia del tratamiento

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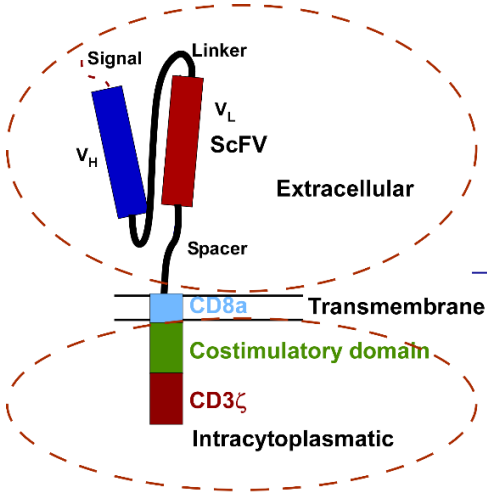
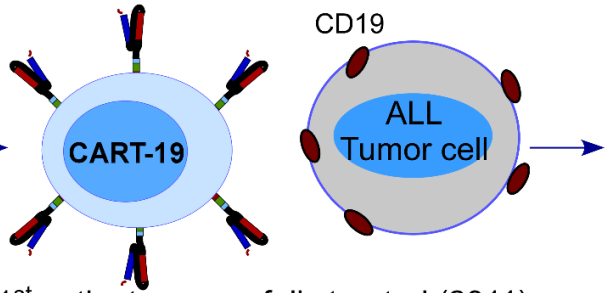
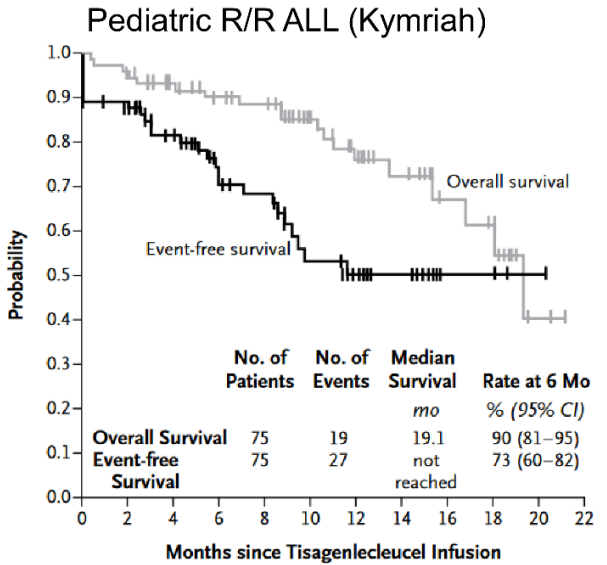
CAR-T cell immunotherapy



2nd generation CAR



1st patient successfully treated (2011)



	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 Mo % (95% CI)
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

1st CARs approved in EU (2018): 1) Yescarta (Gilead/Kite Pharma): CART19 (CD28) 2) Kymriah (Novartis): CART19 (4-1BB)

R/R some types of NHL, follicular lymphoma.
DFS: 51%

R/R B-ALL up to 25 years old, adults R/R DLBCL.
DFS: 62% ALL, 64% DLBCL

Currently: 6 FDA-approved CAR-T cell therapies (CD19 and BCMA) in R/R patients:

Tecartus (MCL, ALL)
Breyanzi (NHL)
Abecma (MM)
Carvykti (MM)

None in solid tumors

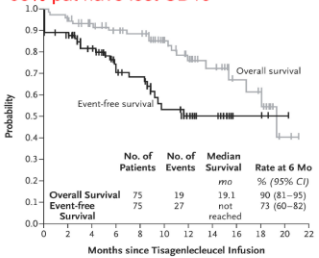
Failure to CAR-T treatment

- Failure of production of autologous CAR-T cells (Universal allogeneic CARs)
- CAR-T cell infusion to the patient
  - Lack of initial efficacy: early disappearance of CAR-T (CAR construct: AICD, immunogenicity)
  - Objective responses
    - Relapses
      - Loss of expression of the target Ag (related to the Ag)
      - Lack of persistence/efficacy of CAR-T cells
    - Permanent responses

Kymriah: CART19 (4-1BB) Pediatric/young ALL

OR= 81%; CR=60%

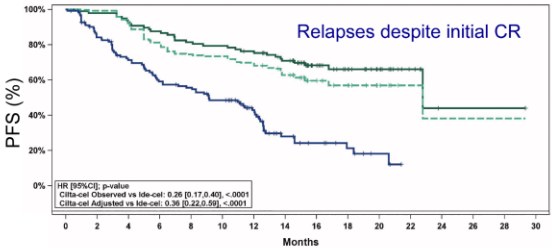
At relapse:
68% pat have lost CD19



Maude SL, et al. NEJM, 2018

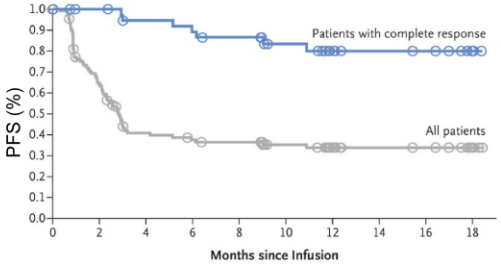
CART-BCMA in R/R MM
CILTA-CEL (JNJ4528) *vs* IDE-CEL: FDA/EMA approved
OR=98, CR=80% OR=73%, CR=33%

At relapse:
Loss of BCMA suspected in 4% pat.



Kymriah in R/R DLBCL

OR= 52%; CR=40%

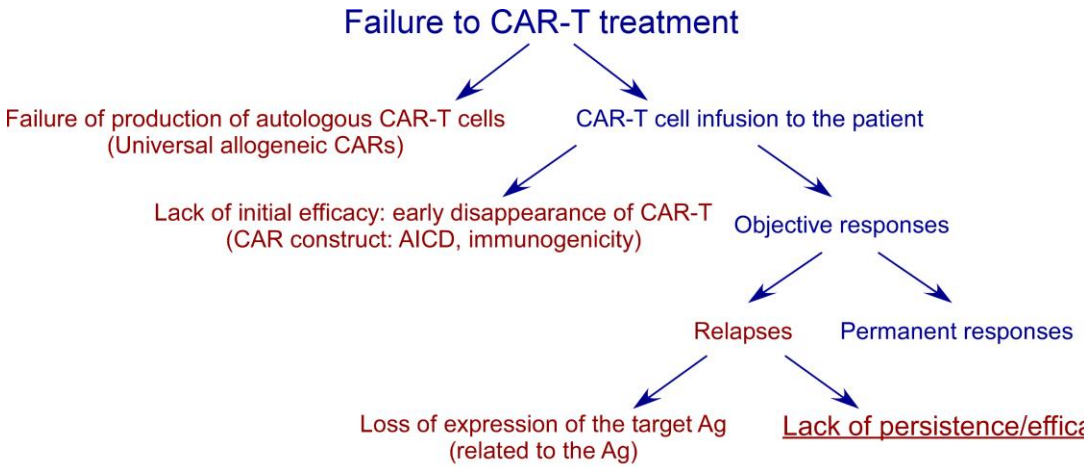


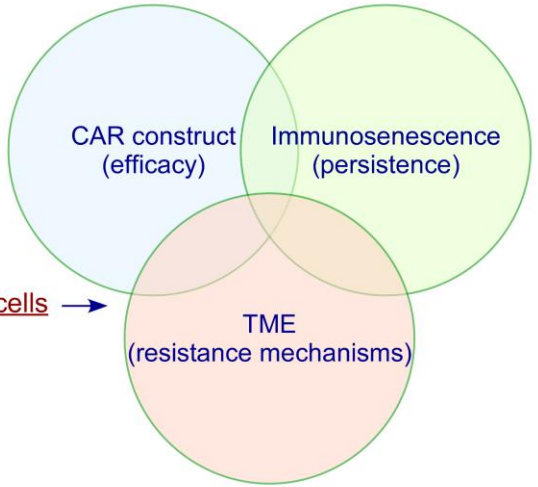
Schuster SJ, et al. NEJM, 2019

Compared to SOC, 2nd line

- No superiority (Kymriah): Bishop, M. et al. NEJM. 2022
- Superiority (Yescarta) Locke, F.L. et al. NEJM. 2022

CAR-T cell immunotherapy: strategies to improve

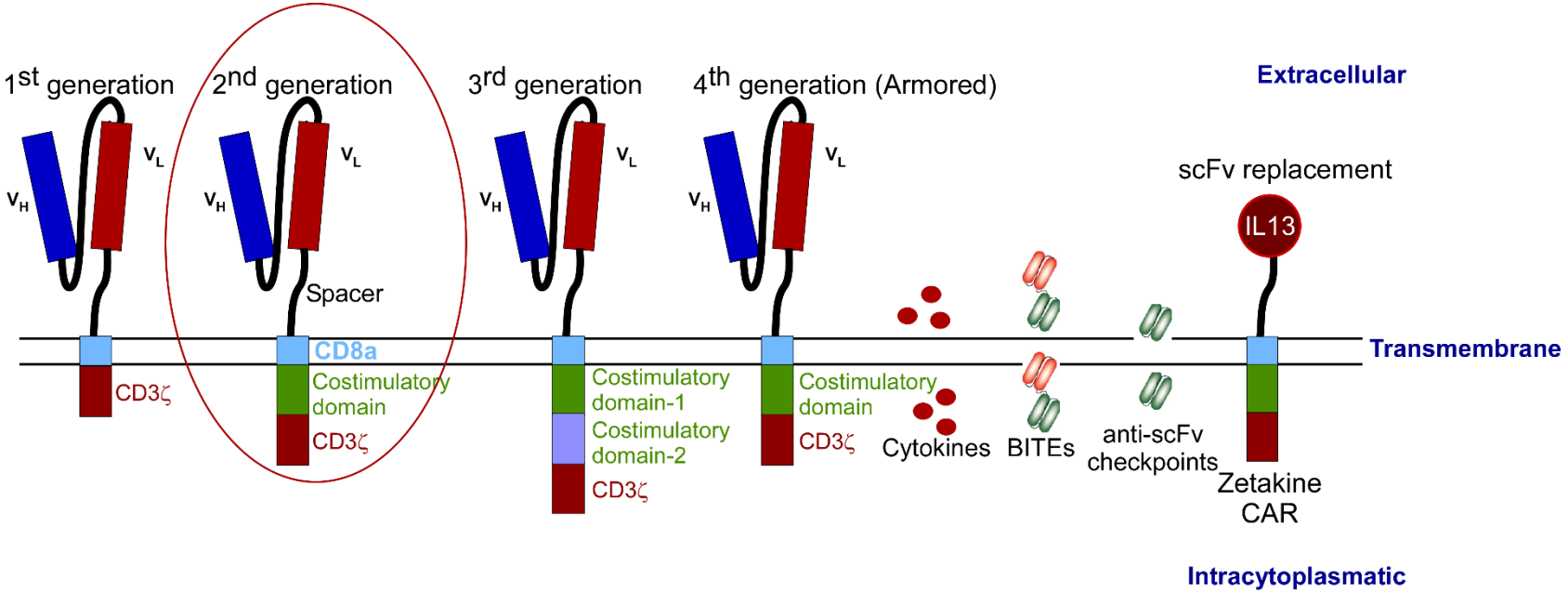




Main targets in our group:

Mature B-cell malignancies (NHL and MM)
Solid tumors (collaborations)

CAR construct: increased efficacy



Source of monoclonal Ab

Hinge/spacer

Transmembrane

Costimulatory domain

Duals, bicistronics, cocktail of CARs, other immune cells

Phenotype of T cell, selection of cell populations

Suicide genes

Source of cell: Universal CARs

Multiple CARs from one construct: SUPRA CARs

Affinity Tunning CARs

Our previous results: CART cells against BCMA in MM (ARI2h cells)

Plasma Cell Disorders

Preclinical development of a humanized chimeric antigen receptor against B-cell maturation antigen for multiple myeloma

Lorena Perez-Amill,[1] Guillermo Suñe,[1] Asier Antoñana-Vildosola,[1] Maria Castella,[1] Amer Najjar,[2] Jaume Bonet,[3] Narcis Fernández-Fuentes,[4] Susana Inogés,[5] Ascensión López,[5] Clara Bueno,[6] Manel Juan,[7] Alvaro Urbano-Ispizua[1,8,9] and Beatriz Martín-Antonio[1,8]

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Ferrata Storti F

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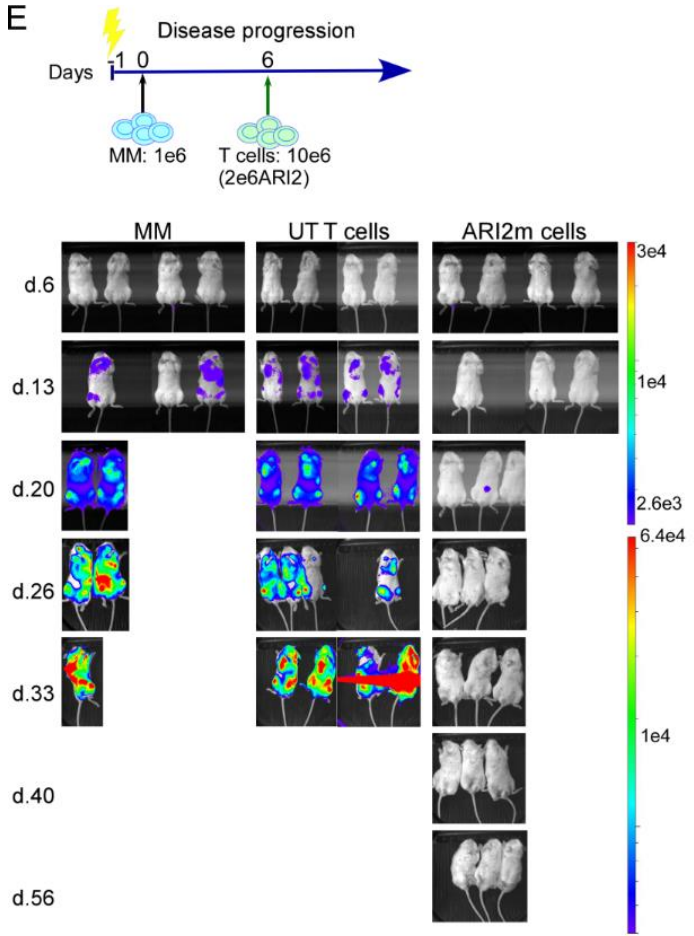
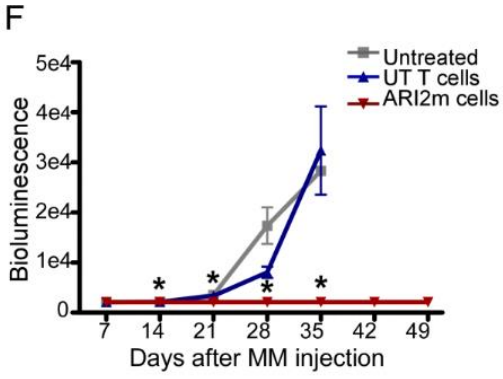
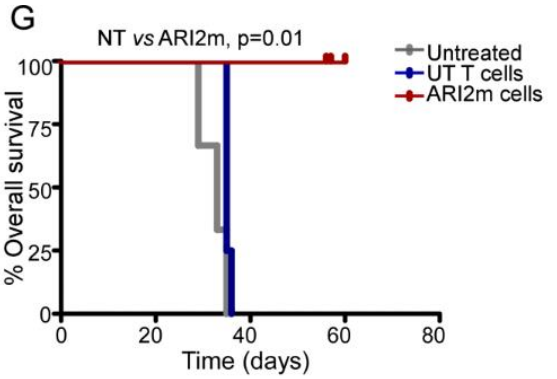
NK cells enhance CAR-T cell antitumor efficacy by enhancing immune/tumor cells cluster formation and improving CAR-T cell fitness

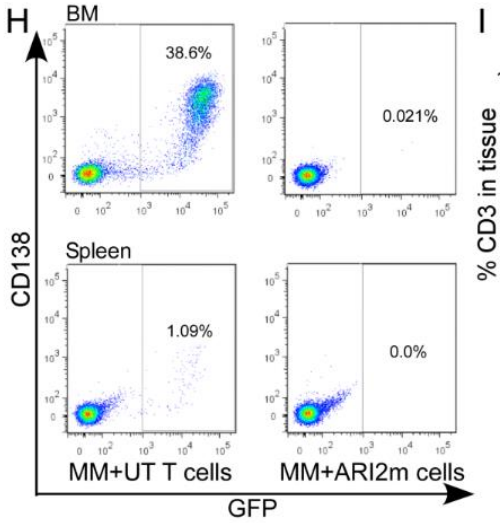
Mireia Bachiller,[1] Lorena Perez-Amill,[1] Anthony Matthew Battram ,[1] Sebastian Ciro Carné,[1] Amer Najjar,[2] Els Verhoeyen,[3,4] Manel Juan ,[5,6] Alvaro Urbano-Ispizua,[7,8] Beatriz Martin-Antonio [9]

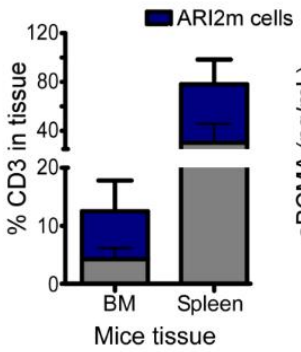
Pre-clinical development of ARI2m and ARI2h cells for the treatment of MM:

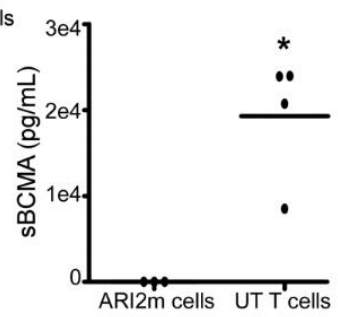




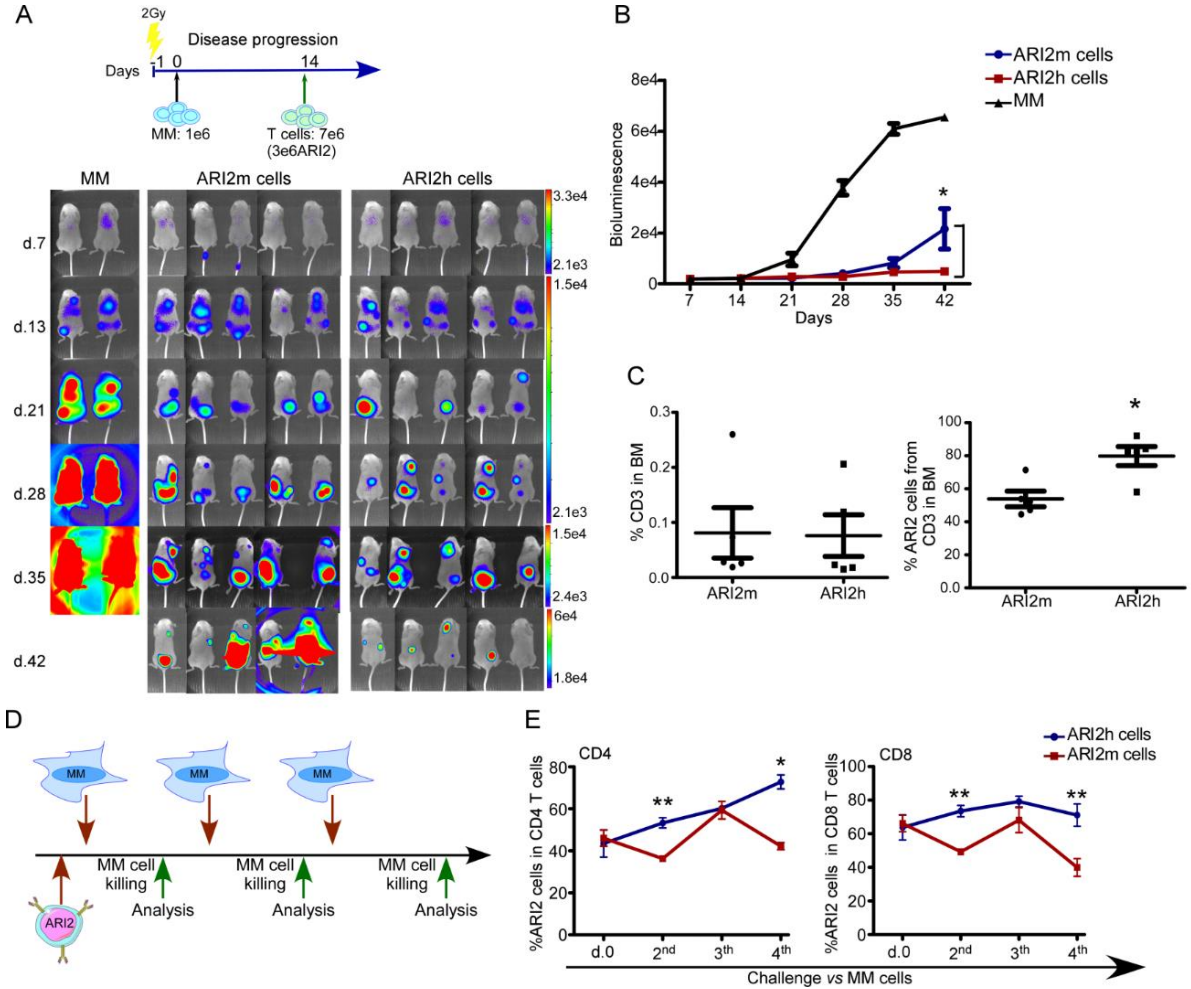




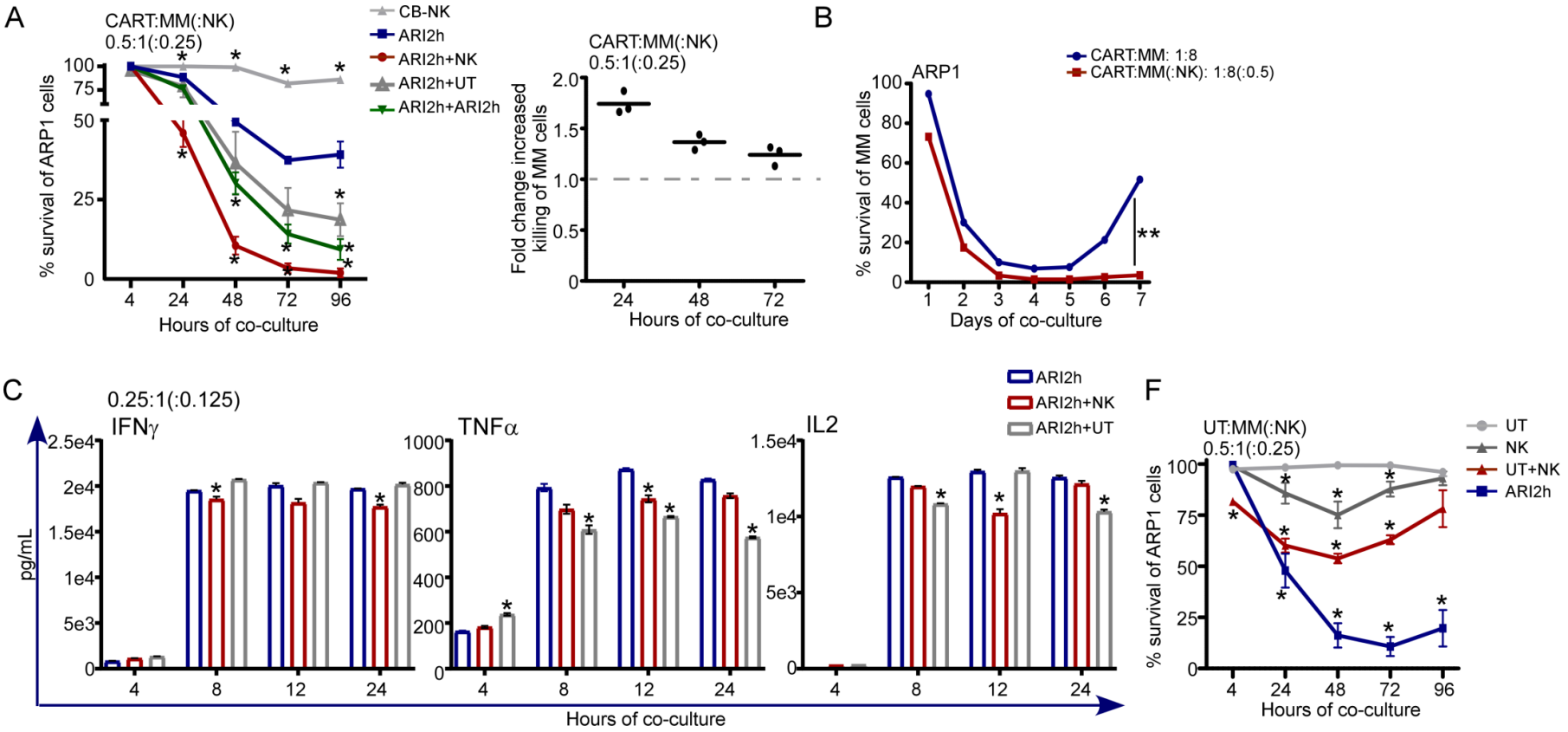




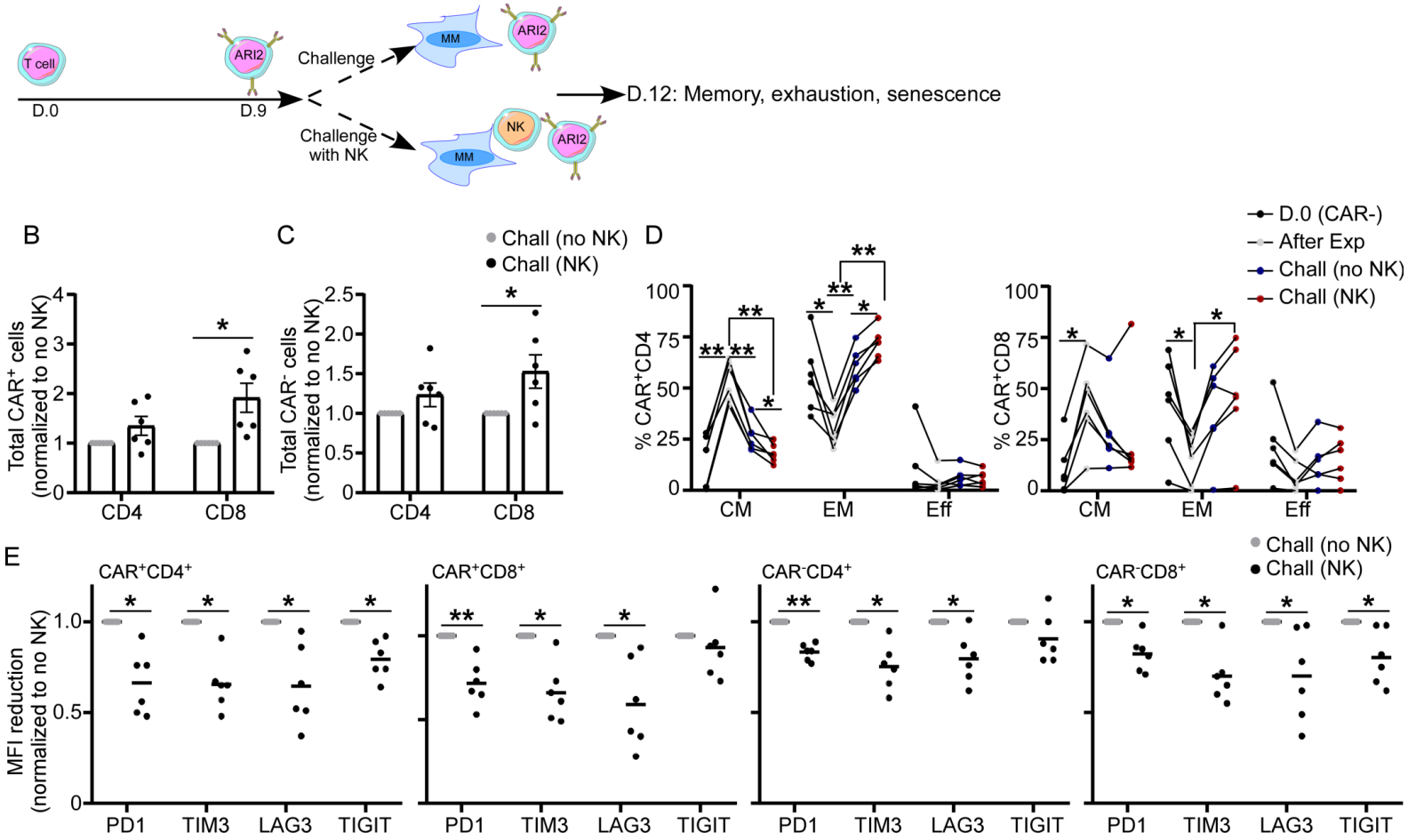
ARI2h and ARI2m in a model of high tumor burden: ARI2h shows superiority to ARI2m:



CB-NK enhances *in vitro* ARI2h and UT T cell efficacy, with no increased cytokine production

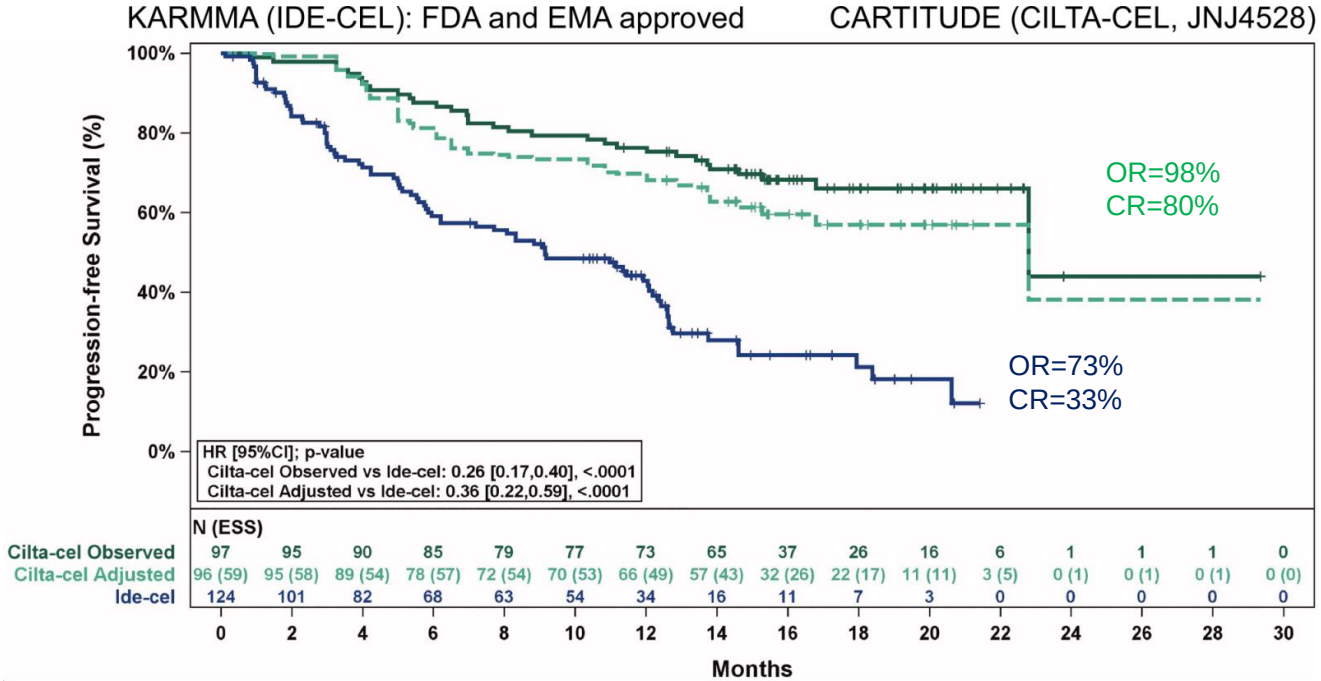


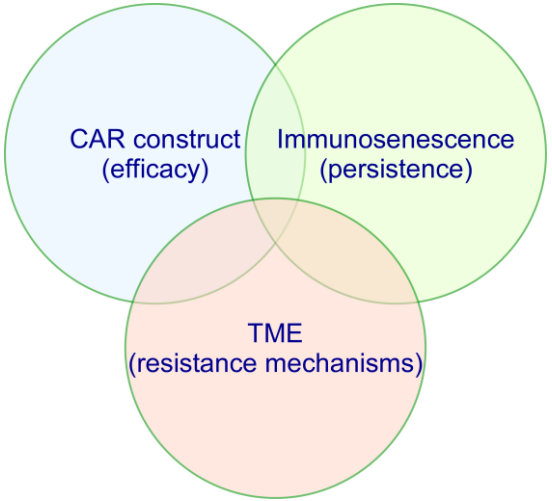
CB-NK increases ARI2h fitness



Immunosenescence: deterioration of the immune system associated to aging

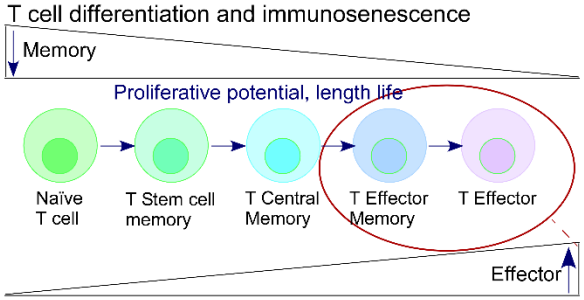
Multiple mieloma: elderly population





Relapses despite initial CR → CAR-T cell disappearance
Dysfunctional T cells

Immmunosenescence: Progressive decline in the immune function associated to aging (Multiple myeloma)



Factors:

Diseases, chronic inflammation, viral infections, cancer

Thymic involution: decreased pool of naïve T cells

In Bone marrow: replacement of cells by adipocytes

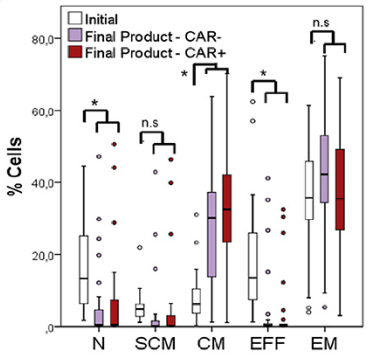
T_{CM}: permantent responses (>10 yrs)

EM and Effector: short life

% Naïve T cells in Healthy children:

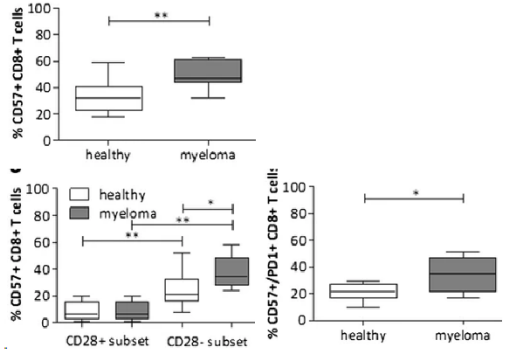
~80%: 0-2 years
~70%: 2-6 years
~60%: 6-12 years
~50%: 18 years

Clinical production of CART cells



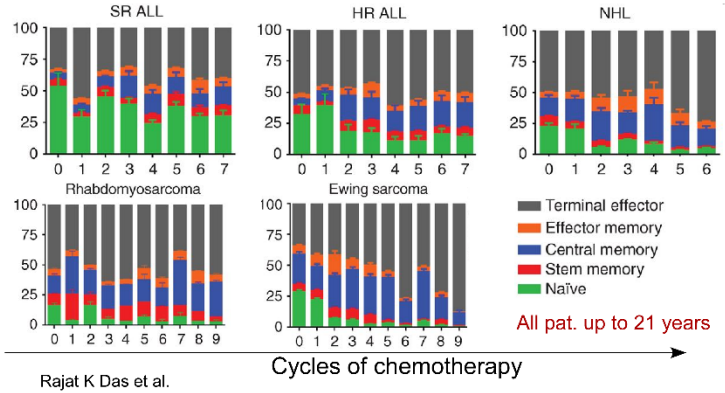
Castella M, et. al.
Front. Immunol,2020

Enhanced in MM
CD8: exhausted and senescent



Claudia Zelle-Rieser, et al.
J Hematol Oncol. 2016

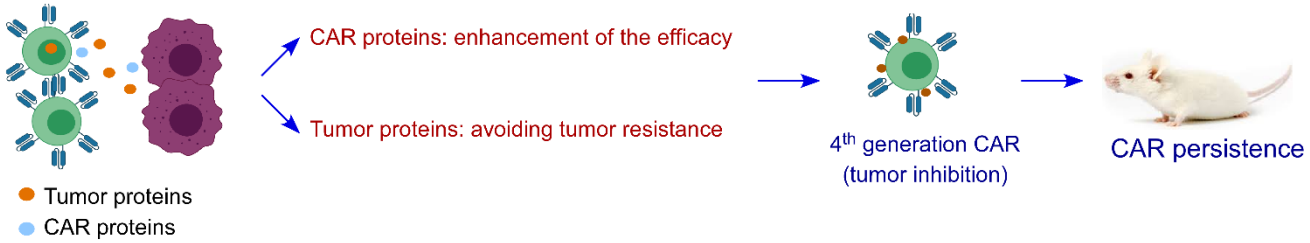
Chemotherapy induced immunosenescence in T cells in cancer patients



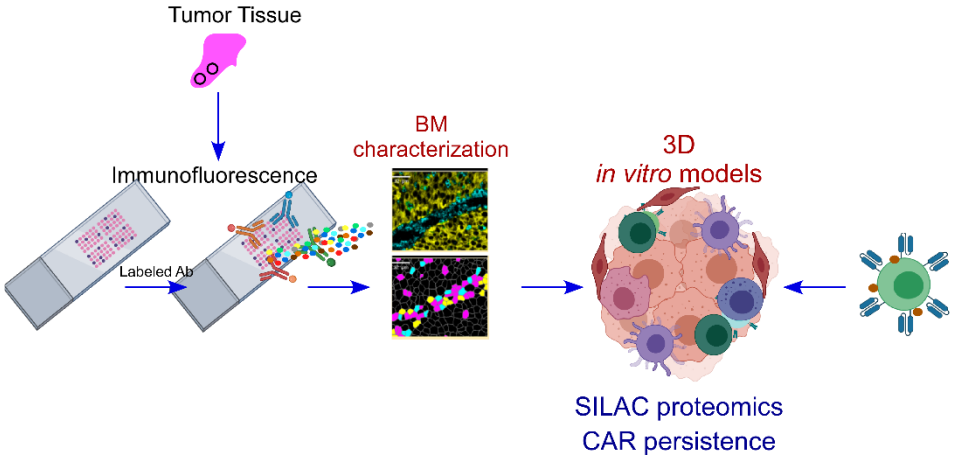
Rajat K Das et al.
Cancer Discov. 2019;9(4)

Tumor microenvironment: resistance mechanisms

1) SILAC proteomics



2) TME characterization



COLABORACIÓN

- *Oferta/Demanda:*

1. Oferta: Producción de células inmunes para inmunoterapia (CARs, NK), modelos NSG in vivo de inmunoterapia.

2. Demanda: mejora en el análisis de datos "omicos", preparación de TMA para posterior análisis del TME, immunocompetent in vivo models