



# ESTRATEGIAS PARA DISMINUIR TOXICIDAD CART

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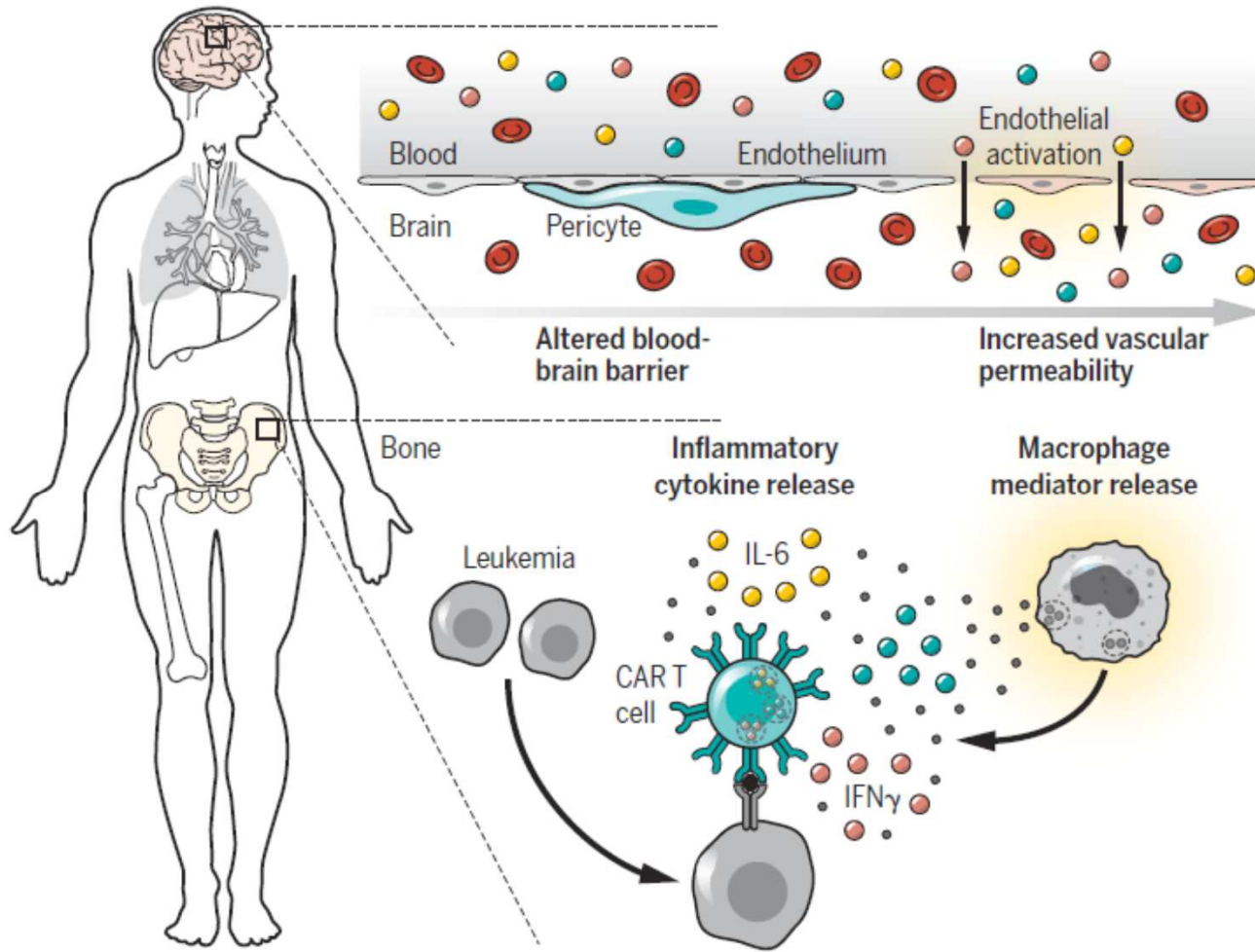
Javier Briones

Servicio de Hematología

Hospital Santa Creu i Sant Pau. Barcelona

[jbriones@santpau.cat](mailto:jbriones@santpau.cat)

# Inmunoterapia CAR-T: Complicaciones



## Neurotoxicidad (ICANS)

- Desorientación
- Afasia
- Delirio
- Convulsiones
- Edema cerebral

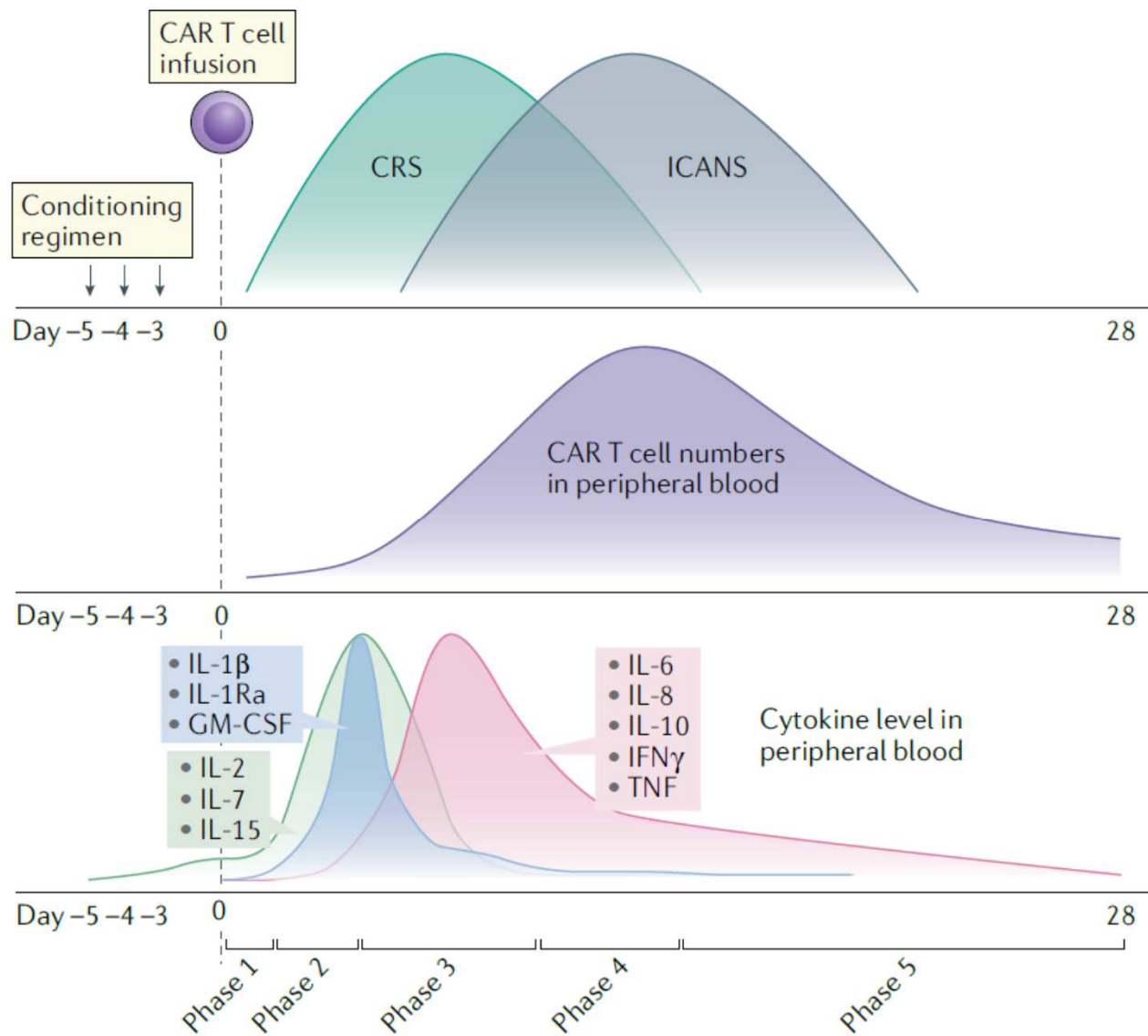
## Sind. Liberación Citoquinas (CRS)

- Fiebre
- Dísnea
- Insuf. Respiratoria
- Hipotensión

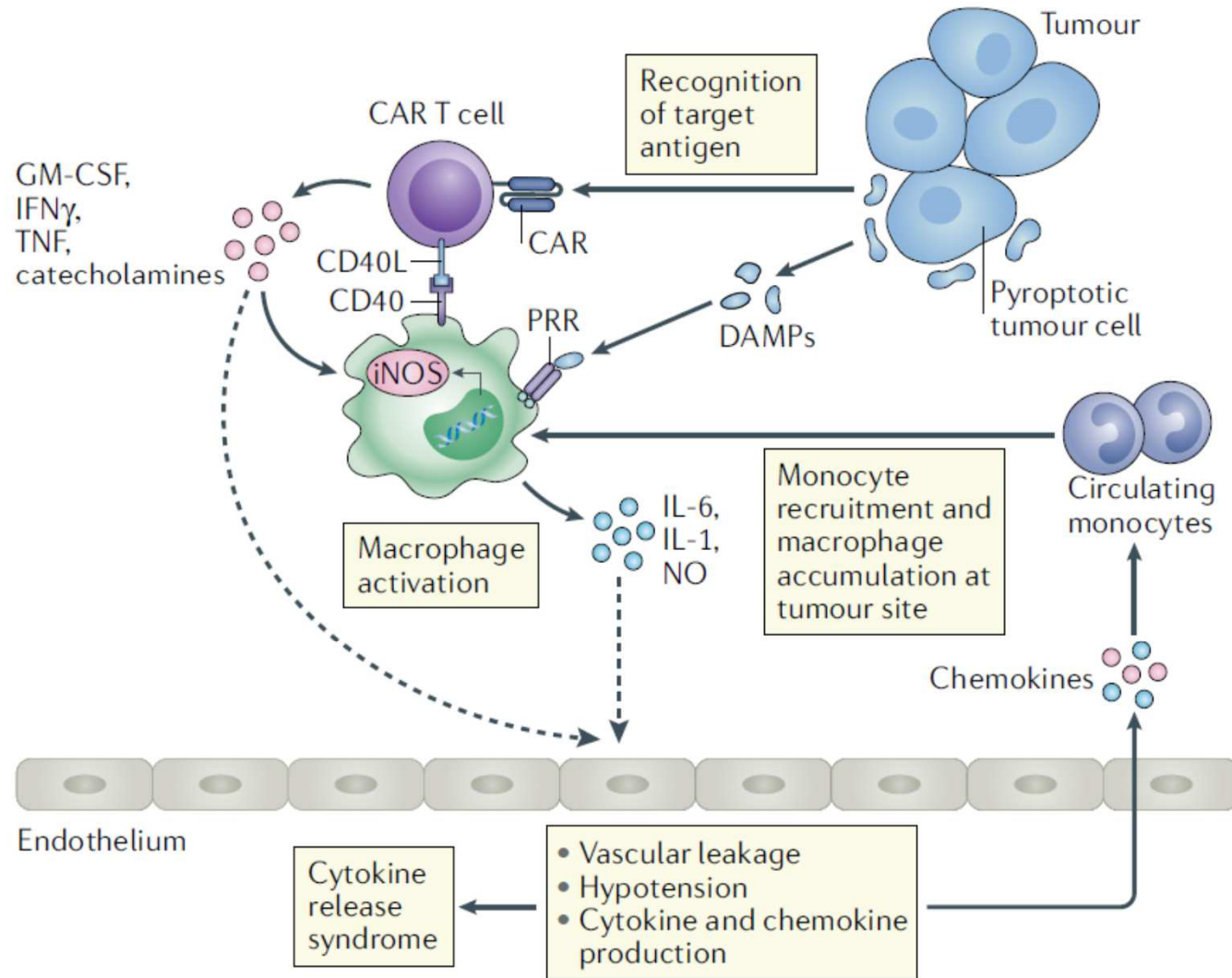
# Complicaciones Terapia CART

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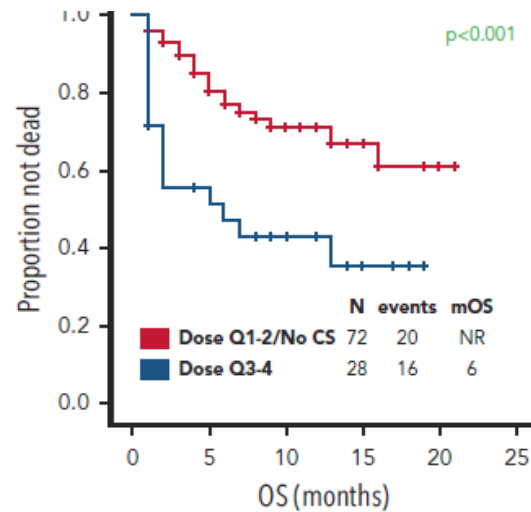
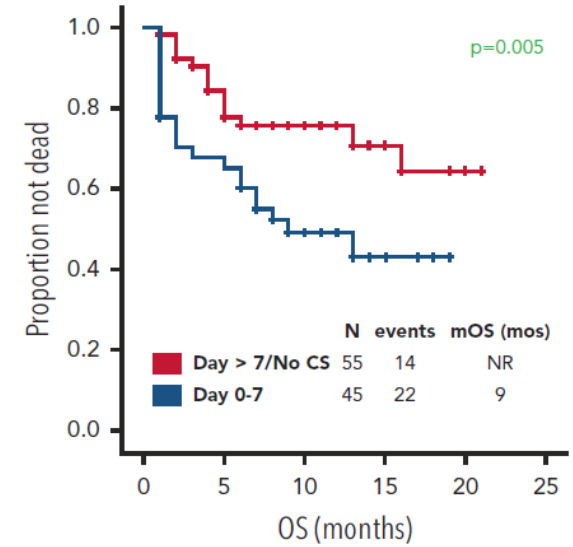
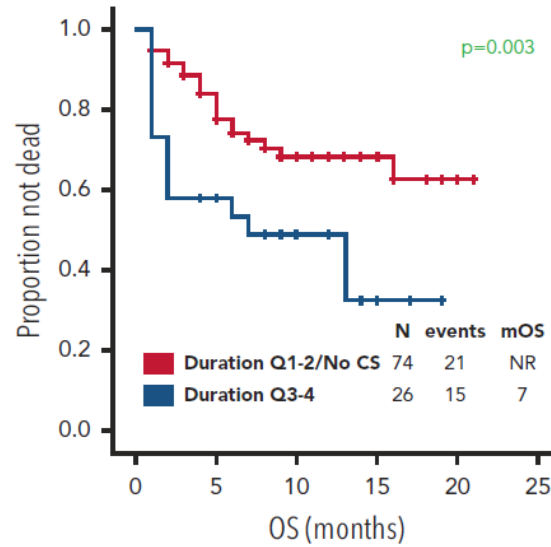
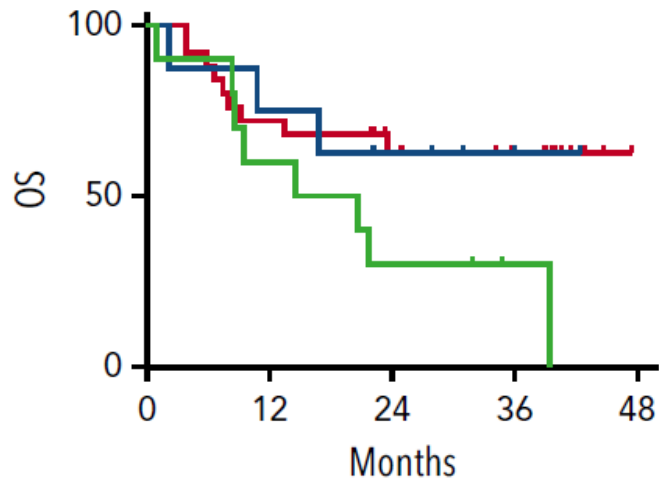
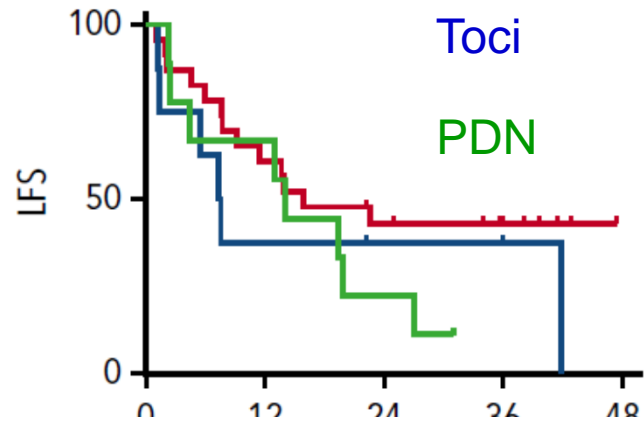
- Complicaciones CART
  - CRS
  - ICANS
  - Infecciones
  - Citopenias
- Factores implicados en Toxicidad CART
  - Factores clínicos
  - Diseño CART
  - Sistemas de producción CART
  - Nuevos diseños: 4ª Generación
- Estrategias de prevención y Tratamiento
- Nuevas estrategias terapéuticas



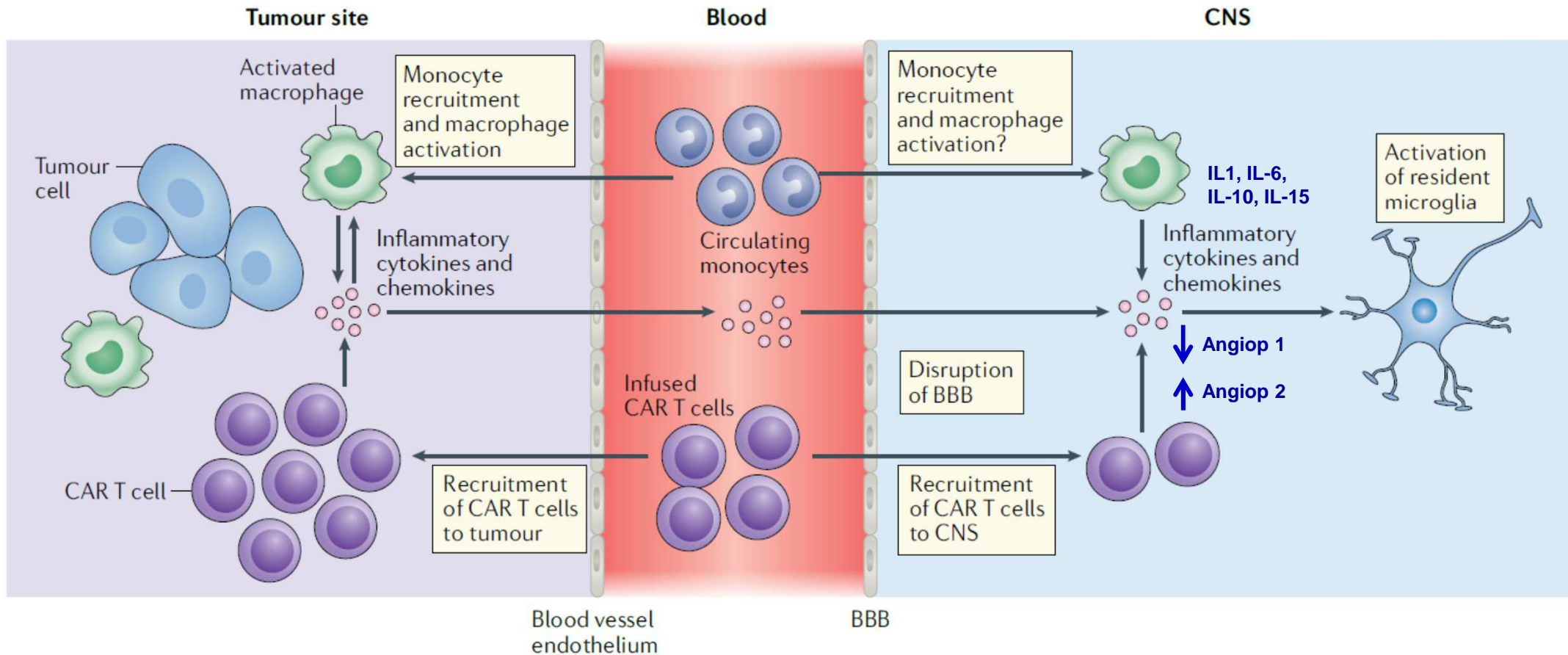
# Physiopathology of CRS



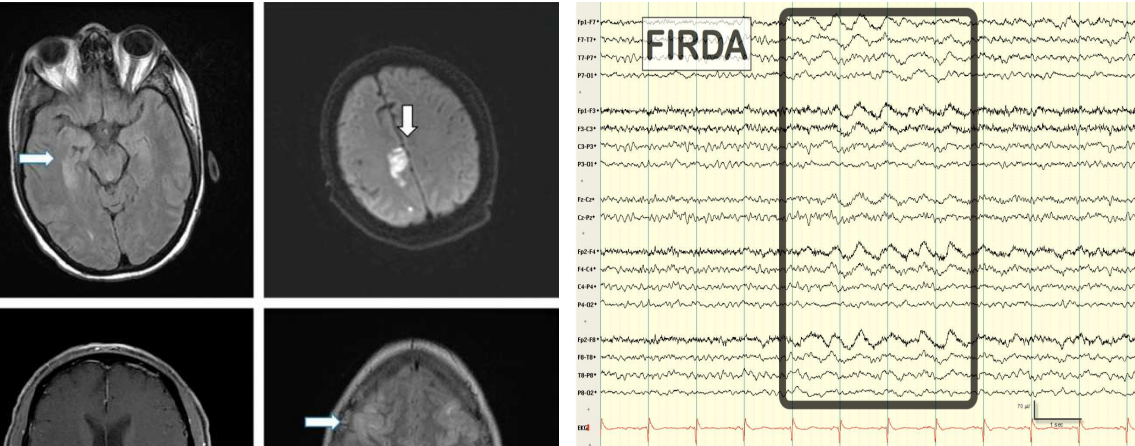
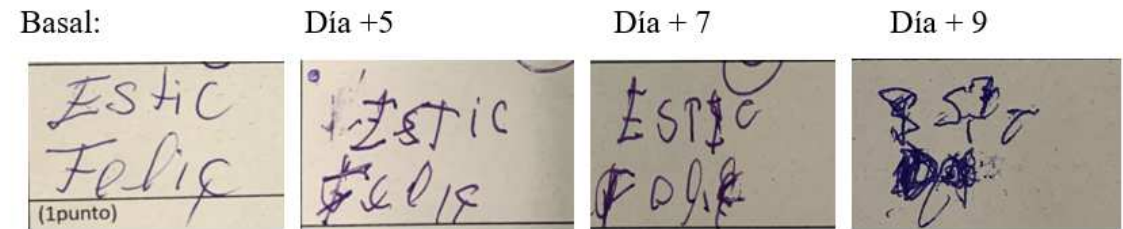
# Impact of Steroids/Toci on CART Outcome: Dose and timely dependant



# ICANS pathophysiology



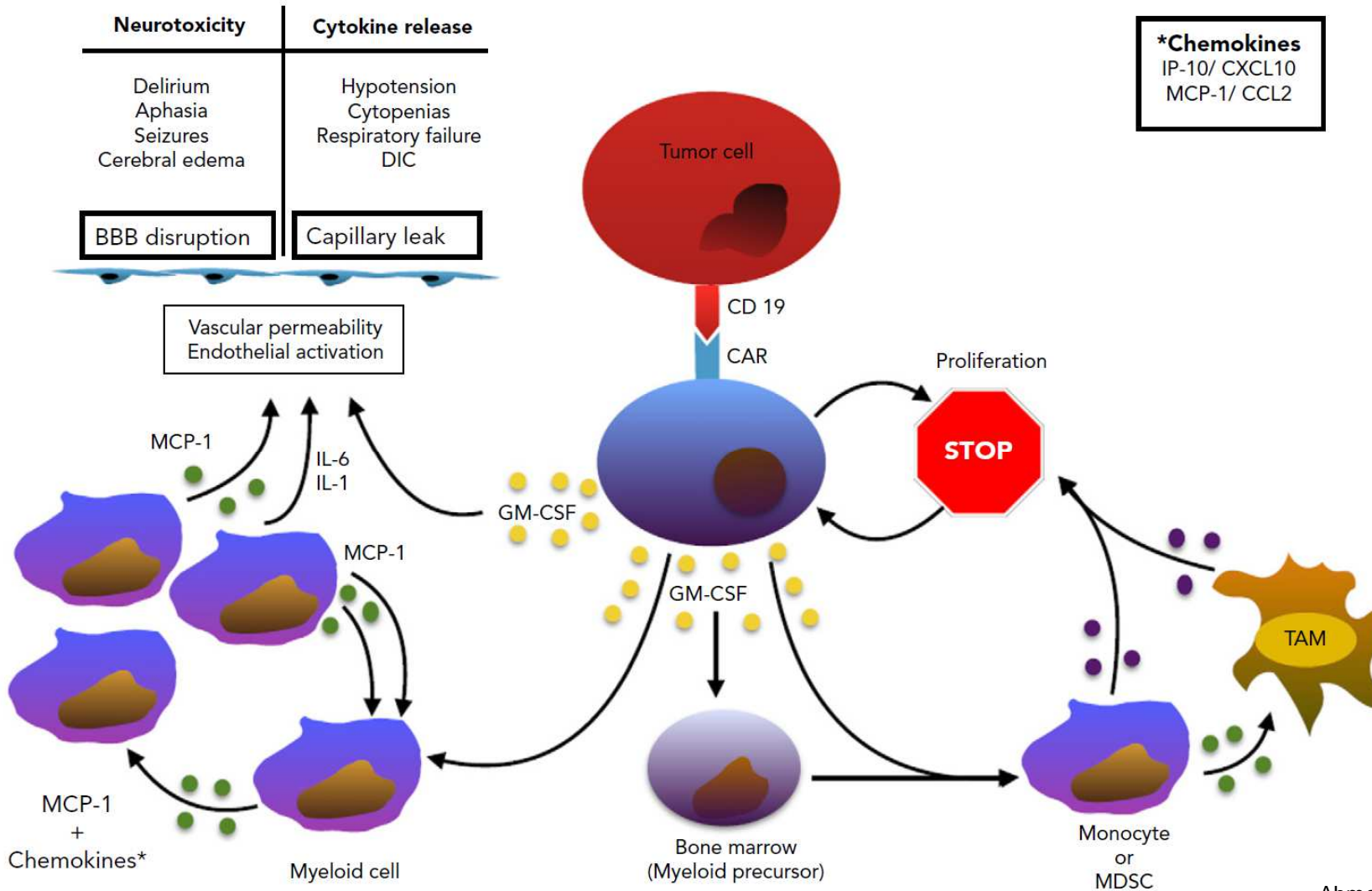
# Clinical Factors associated to ICANs



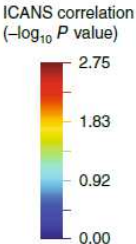
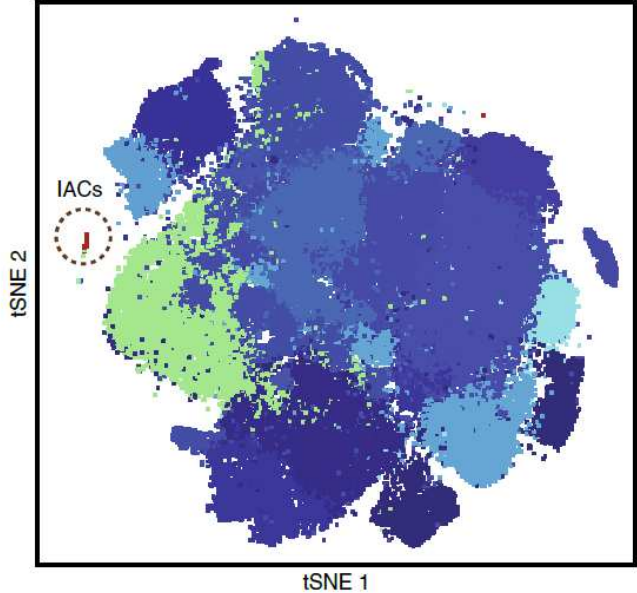
- Tumor burden
- CART expansion (IL-15 peak)
- Previous CRS (severity of ICANs)
- Low platelet counts (< 50.000)
  - Low ratio angiopoetin 1:2
- High peak ferritin (severity of ICANs)
- Brain macrophage activation



# Role of myeloid/macrophages on ICANs



# Predicting factors for ICANs: Rare Monocyte-like cells (IACs)



	Pts with IACs
ICANS gr 0-2 (n=22)	9%
ICANS gr 3-4 (n=18)	61%

	IAC	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
<i>IL1B</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>SIRPA</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>IL8</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>LILRB4</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CD68</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CD8B</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CD4</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CD3E</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CAR</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>CD14</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>FCGR3A</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
<i>FCGR3B</i>	●	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

# Complicaciones Terapia CART

- Complicaciones CART: Mecanismos
  - CRS
  - ICANS
- Factores implicados en Toxicidad CART
  - Diseño CART
  - Métodos de producción CART
  - Nuevos diseños: 4ª Generación
- Nuevas estrategias terapéuticas

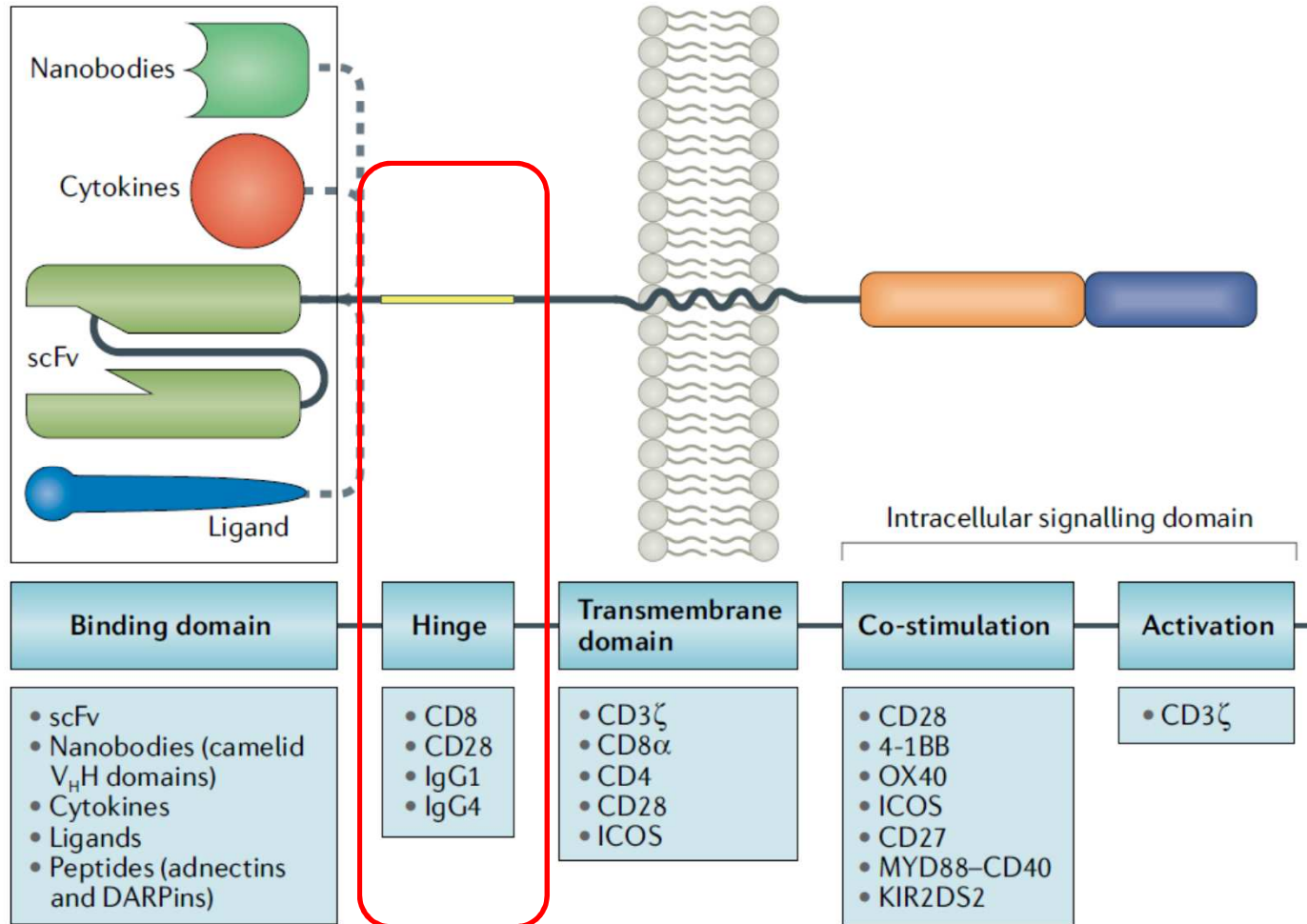
## CART19 for DLBCL: Distinct grades of toxicities and different constructs

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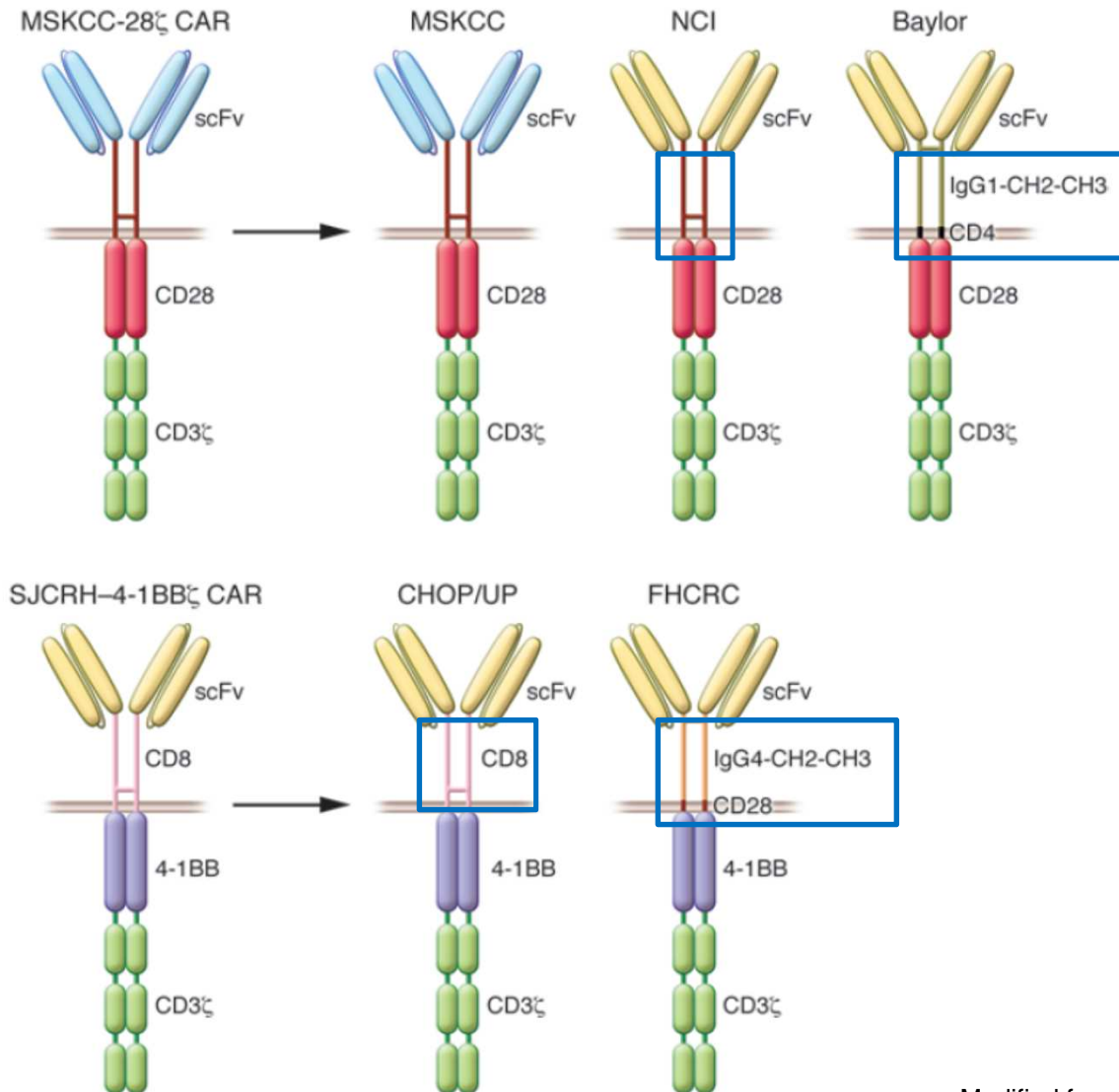
	Axi Cel	Tisa Cel	Liso Cel
N	108	111	269
Construct	CD28-z	4-1BB-z	4-1BB-z
CRS	102 (92%)	64 (58%)	113 (42%)
CRS gr 3-4	12 (11%)	24 (22%)	6 (2%)
ICANs	72 (69%)	23 (21%)	80 (30%)
ICANS gr 3-4	35 (32%)	13 (12%)	27 (10%)

Schuster et al. NEJM. 2019  
 Nastopoul et al. JCO 2020  
 Locke et al. Lancet Oncol 2019  
 Abramson et al. Lancet 2020

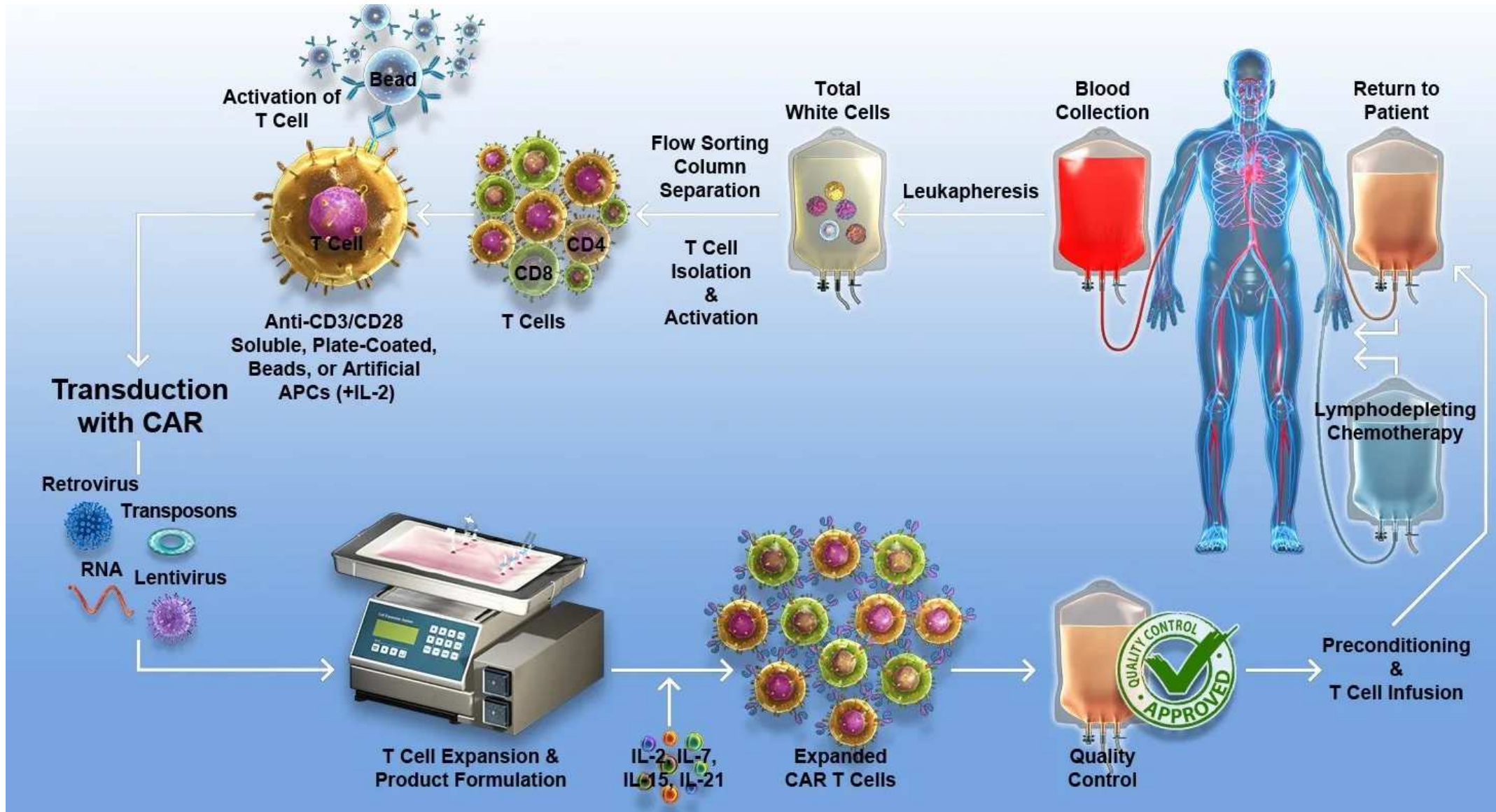
# CAR Components and Function



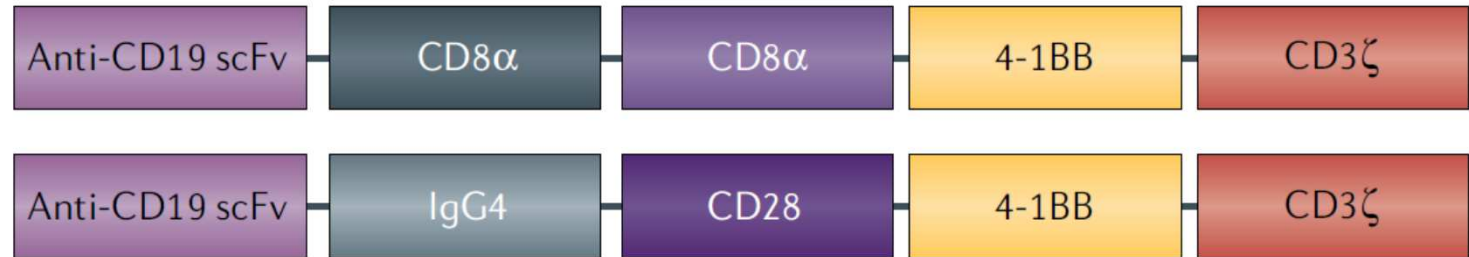
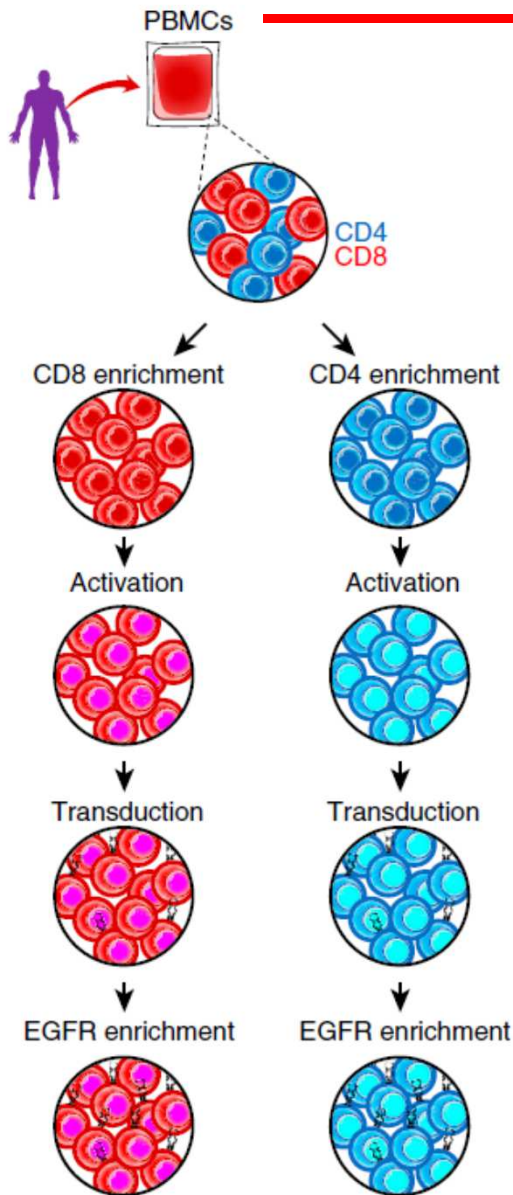
# Different CART-Hinge design Modalities



Modified from Sadelain. JCI. 2015



# Incidence and severity of CRS and ICANS: Role of CD4:CD8 Ratio



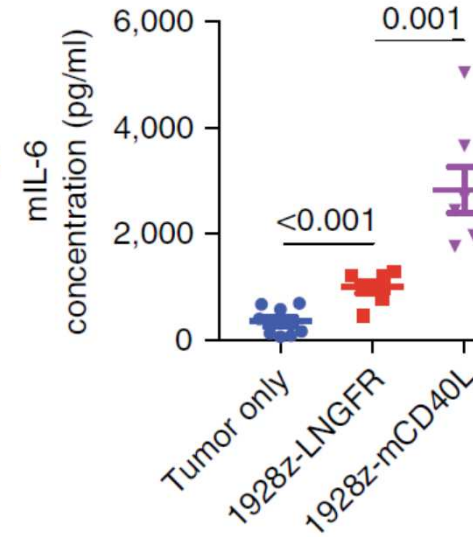
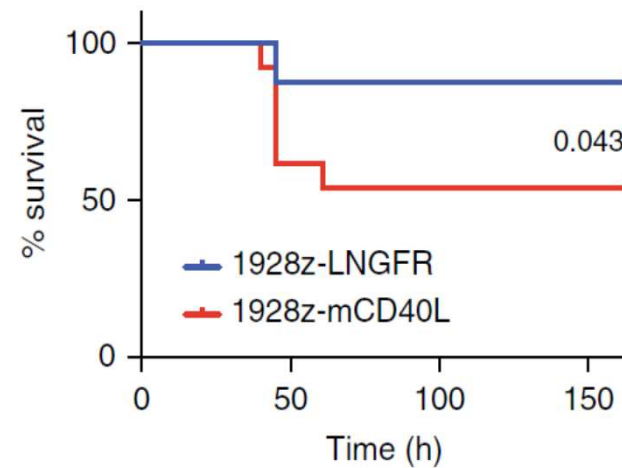
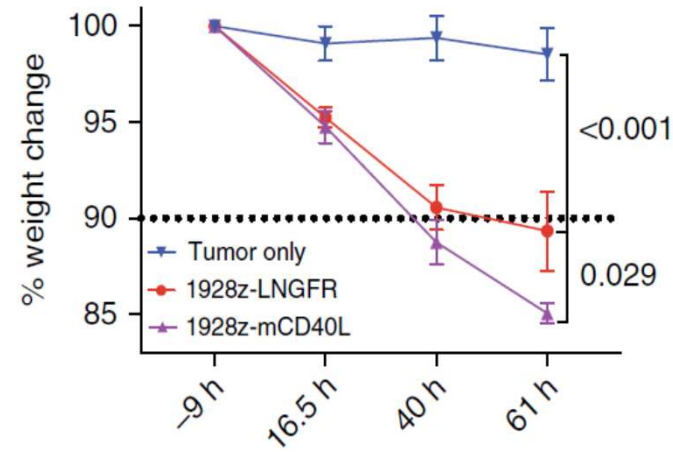
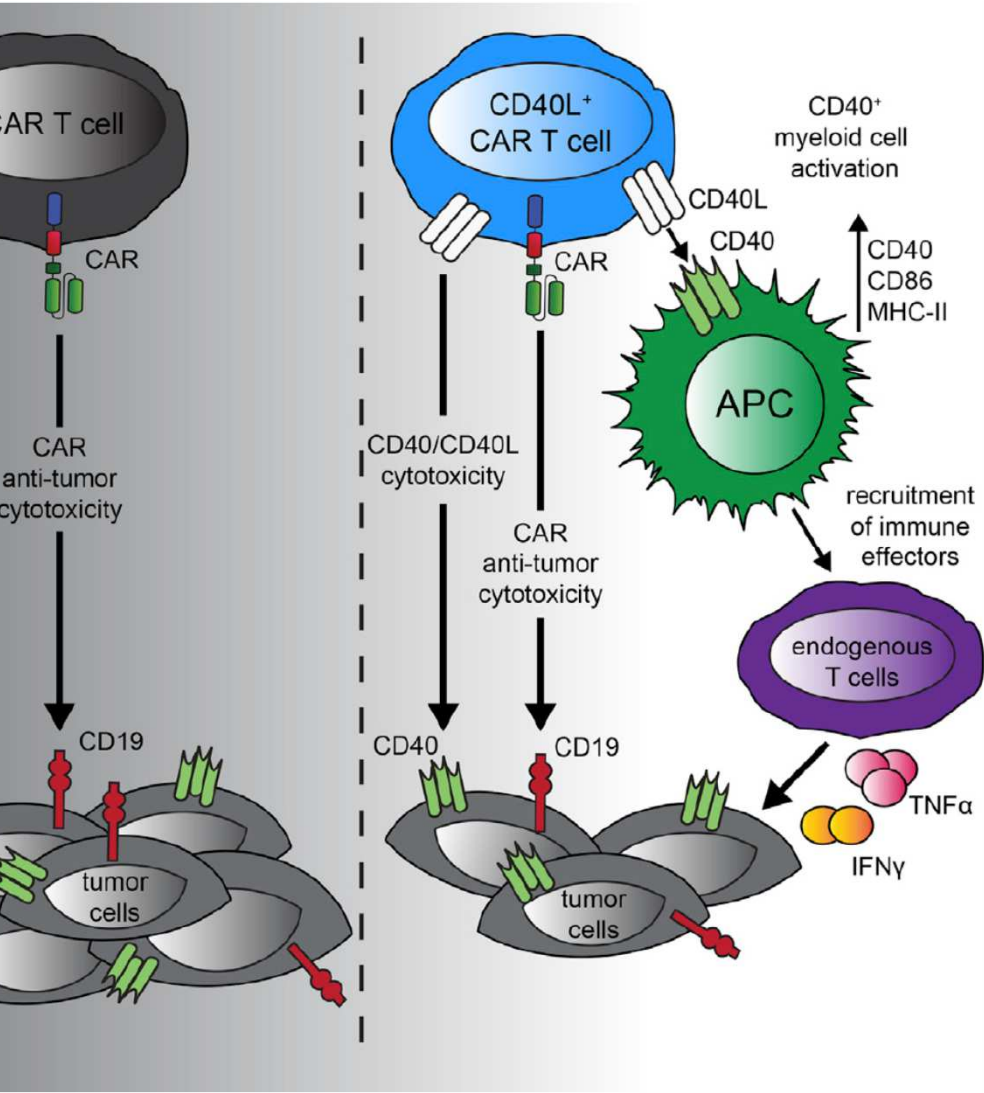
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Ratio CD4:CD8: 1

Abramson et al. Lancet 2020  
Schuster et al. NEJM 2019



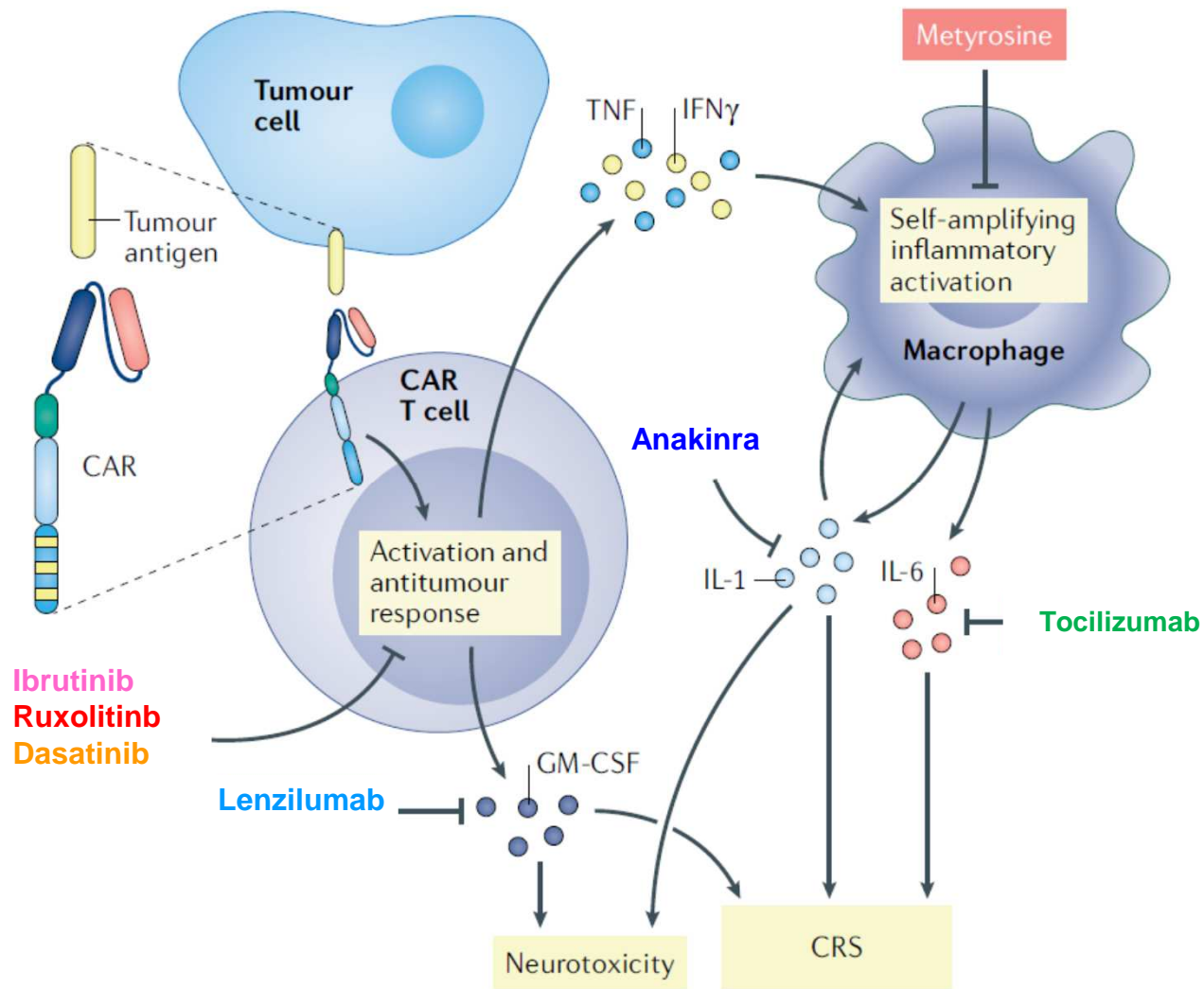
# CART New designs and Toxicity: "dangerous liaisons" (CART19-CD40L)



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- **Nuevas estrategias terapeuticas**

# Novel Therapies for CRS/ICANS



Modified from Larson and Maus.  
Nat Rev Cancer 2021

# IL-6 Signals through JAK/STAT Pathways: Role of Ruxolitinib for CRS Prevention

NSG Transgenic for SCF, IL3 and GM-CSF

