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CAR-T cells as an Anticancer Therapy: current challenges and emerging opportunities

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Introduction

Infusion of chimeric antigen receptor-genetically modified T cells (CAR-T cells) have shown outstanding results in clinical trials with patients suffering from relapsed or refractory B-cell malignancies. However, besides the clinical benefit established for these therapies, CAR-T cells are associated with unique acute toxicities, mainly **Cytokine Release Syndrome** and **Neurotoxicity**. The aim of this work is to present some of the key points that are currently related to CAR-T cell therapies, such as the major risk factors related to the life-threatening toxicities (cytokine release syndrome and neurotoxicity); the emerging applications from both large pharmaceutical companies and small/medium biotechnology industries and the progresses made so far in CAR-T cells-based therapies including the latest innovations in CAR design.

CAR-T cells

Genetically engineered autologous or allogenic T cells to express a **chimeric antigen receptor** (CAR). The CAR enables the redirection of T-cells' cytotoxic activity to a specific tumor antigen. CAR-T cells are targeted to cancer cells independently of MHC expression and HLA haplotypes.

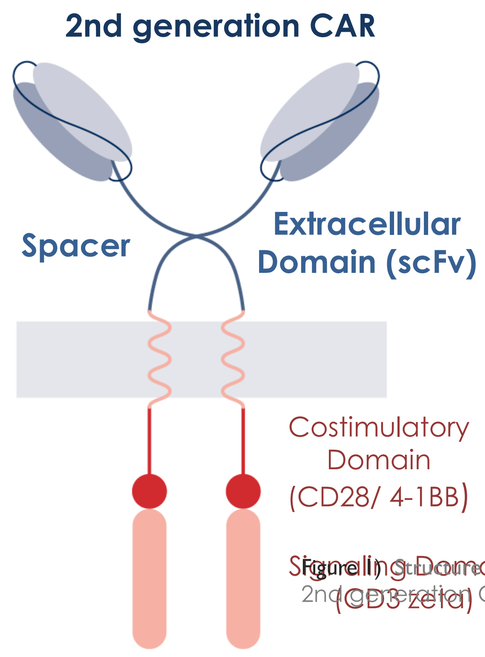

Figure 1) Structure of a 2nd generation CAR

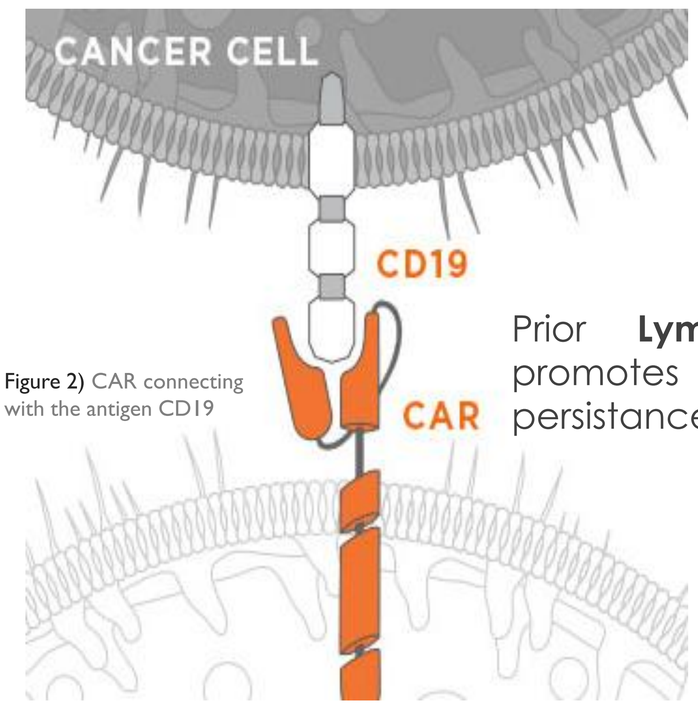

Figure 2) CAR connecting with the antigen CD19

Prior **Lymphodepletion Regimen** promotes peak expansion and persistance of CAR-T cells *in vivo*.

High response rates in the treatment of **relapsed or refractory CD19+ B-cell malignancies** with **CD19 specific CAR-T cells**:

Acute Lymphoblastic Leukemia (r/r B-ALL),
Non Hodgkin's Lymphoma (r/r B-NHL),
Chronic Lymphocytic Leukemia (r/r B-CLL).

First-in-class Products

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion — NOVARTIS

Approved for the treatment of **r/r B-ALL** on 10/08/2017.

Second indication (r/r DLBCL) approved on 01/05/ 2018.

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion — Kite, A GILEAD Company

Approved for the treatment of **r/r B-NHL** on 03/10/2017.

Emerging Pipeline

cellectis — Allogenic T cells genetically edited by **TALEN® technology**

TC BIOPHARM — Autologous and Allogenic **delta gama (δγ)** T cells

Life -threatening Toxicities

Cytokine release syndrome (CRS)

✓ **Systemic inflammatory response.**

✓ **Risk Factors**: tumor burden, antigen expression level, *in vivo* peak expansion promoted by prior lymphodepletion.

✓Key role of IL-6 and effectiveness of anti-IL-6R receptor monoclonal antibody **tocilizumab.**

New data from study conducted by Norelli *et al*. (2018) revealed that **monocytes** are the major sources of IL-6 (and IL-1) during CRS, rather than CAR-T cells. According to a time-course analysis, the release of IL-1 preceded IL-6. As IL-1 is capable of inducing the secretion of IL-6, is IL-1 the primary cause of CRS?

IL-1R antagonist **Anakinra** abolished CRS.

Neurotoxicity (NTX)

✓ Severe CRS leads to severe NTX.

✓ **Risk Factors**: infused dose of CAR-T cells, tumor burden and preexisting neurologic comorbidities.

✓ Key role of **IL-6** - early plasmatic peak leads to NTX severe.

Study conducted by Gust *et al*. (2017) provides evidence for cytokine-mediated **endothelial activation:**

Endothelial activation (increases in serum levels of ANG2 and Von Willebrand factor) → blood-brain barrier (BBB) permeability increased → Transit into the CNS of serum cytokines and CAR-T cells → Secretion of IFNγ and TNFa, induces pericyte stress → Loss of cerebral vascular integrity and disruption of BBB

The Future of CAR-T cells

The SUPRA CAR

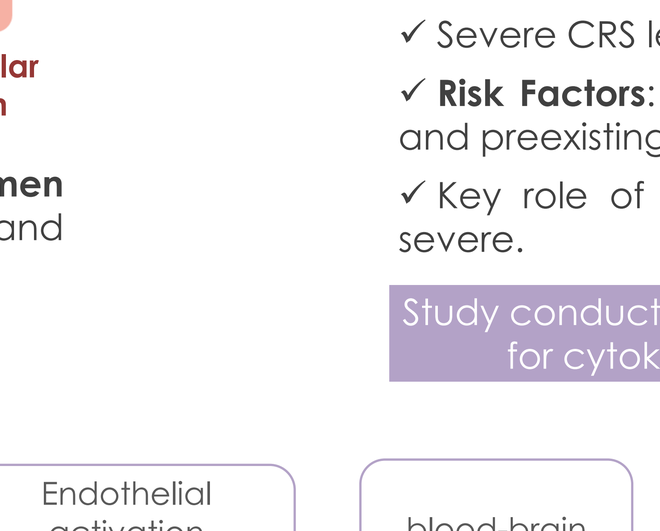

Figure 3a) SUPRA CAR Structure (adapted from CHO *et al.*, 2018)

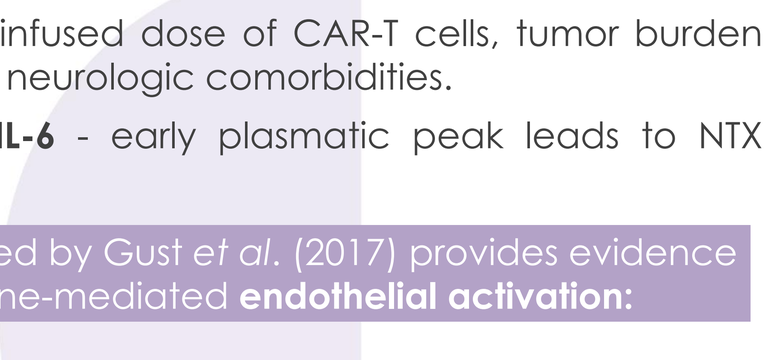

Figure 3b) Multi-antigen recognition strecture adapted from CHO *et al.*, 2018)

✓ Split, universal, and programmable (SUPRA) CAR system;
✓ Variable antigenic specificity without further genetic manipulations;
✓ Advanced control features implemented into a single system in order to promote *in vivo* security.

Conclusion

✓ CAR-T cell-based therapy as a new valiable option for the treament of relapsed or refractory B-cell malignancies;

✓ First products approved in 2017 and new candidates are emerging;

✓ Safety challenges yet to be overcome - focus on the management of life-threatening toxicities.

Acknowledgments
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