Cutting-Edge Health Technologies: Opportunities and Challenges
Landscape & Perspectives for Health Outcomes.

How CAR-T is likely to impact public health ... the "Spanish model"?

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Immunotherapy section.
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Immunotherapy platform H Sant Joan de Déu / BST
Thursday, October 31th 2019 (10:30)
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Conflicts of interest

• No conflict with commercial interests or companies, except in what corresponds to educational talks sponsored by some companies and recent participation (S-5) as member of an Oncology Advisory Board of Grifols no-related with CAR-T therapy.

• Responsible of production of CART product (ARI-0001 cells) in patients with B-cell malignancies (CART19-BE-01 trial). Dossier in preparation for approval by AEMPS … but no-personal (economic) profit from it.
Tumoral cells

Immune system: T-cell

Changes in microenvironment

Immune memory (persistence)

Cytotoxicity

Author's figure
Immune System

- Internal (we already have it) and holistic.
- Continuously effective (from infections to tumours).

Specific

CHANGE OF PARADIGM!
ANTITUMORAL CELL-IMMUNOTHERAPY

TA Vaccines
DCs
SCT / DLIs Allo-recognition
TILs
NK
CARTs
TcR

Knowledge+ Infrastructures (Clean rooms) + Regulation / Quality

Author figures
What is a CART?

T-cells engineered with CARs (Chimeric Antigen Receptor)

“Cytotoxic” T-cell

Signaling domains (CD3ζ, CD28, …)
CAR = Chimeric Antigen Receptor

1ª descripción “T-bodies” by Prof Zelig Eshhar (1995), Weizmann Institute of Science, Israel.
An autologous product as a “live drug”
CAR production

UNDER GMP CONDITIONS

PATIENT

Leukoapheresis

Blood

LYMPHOCYTES

Lymphocyte transduction of CAR

CART+ lymphocytes against tumor

CART infusion

Cryopreservation

T-cell expansion by CD3 + CD28 beads

Cell expansion

CART+ lymphocytes against tumor

Cell therapy => Advanced therapy product = “Drug”
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.
2\textsuperscript{nd} generation CAR

scFv anti-CD19 = Tumor Antigen Recognition

Hinge + Transmembrane (CD8a)

Costimulatory domain (CD137 / 4-1BB = 2\textsuperscript{nd} signal / 3\textsuperscript{rd} signal)

Signaling domain
Success of CARs: Patients n=185 (now near 1,000)

Diseases
- Relapsed
- Refractory
- Heavily pretreated

Overall response
- Acute lymphoblastic leukemia (ALL) 81%/76%
- Chronic lymphocytic leukemia (CLL) 41
- Non Hodgkin lymphoma (NHL) 46

Approvals by FDA & MDA as “live drugs” -> Commercial production

PATIENTS (Public Health Systems)

“Conditioned” CENTRALIZED approval

2010 2017-18

Schubert ML/ Schmitt M Hum Gene Ther. 2016 Jul 31
Barcelona: From “our patients” to “our” CAR ANTI-CD19: ARI-0001

LENTIVIRAL SEQUENCES

EF-1 PROMOTER

CD8a (signal peptide)

scFv A3B1

CD8a (transmembrane)

CD137 / 4-1BB (Signaling domain)

CD3ζ (Signalling domain)

LENTIVIRAL SEQUENCES

gDNA / lentivirus

mRNA

CAR Protein (transmembrane)
CAR production

Coding sequence for the chimeric receptor antigen: CAR

\[\text{CarT} + \text{CAR production}\]

PBMCs → RNA → RT-PCR → PCR products → Construct

<table>
<thead>
<tr>
<th>Prime sequence for CAR antigen:</th>
<th>scFv</th>
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<tbody>
<tr>
<td>CAR scFv</td>
<td>V(<em>{\text{m}}) V(</em>{\text{l}})</td>
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<table>
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<tr>
<th>Transmembrane</th>
<th>4-1BB</th>
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<tr>
<td>CD3(\zeta)</td>
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PBMCs: Peripheral Blood Mononuclear Cells

PATIENT

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<th>Blood</th>
<th>Leukoapheresis</th>
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LYMPHOCYTES

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<th>Monitoring</th>
<th>CART infusion</th>
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Lymphocyte transduction of CAR

T-cell expansion by CD3 + CD28 beads

UNDER GMP CONDITIONS

HEK-293t cell line

Lentivirus

Vector

Packaging

Construct

CART infusion

Cell expansion

Cryopreservation

CART+ lymphocytes against tumor

Monitoring
GMP facilities at HCB - UB

Cell Clean rooms

Vector Clean rooms
Phase I ALL/NHL-CLL ARI-0001 (anti-CD19)

Production of CAR vector (Lentivirus)

Lymphoapheresis

HCB/UB

Production of CAR-T

Buorreactor

HCB

CAR-T infusion

HCB

HSJD
1.- Role of hospitals in developing new technologies:

"Academic" products of cell immunotherapies (specially CARTs) are possible (at least in Spain)!!!
2. - CAR-T therapy in practice: ACADEMIC + INDUSTRIAL CARTs (collaboration)

**Phase II LLA ARI001 (CD19)**
- Production of CAR vector (Lentiv)
- CAR-T Production
- Biorreactor
- HCB
- N=11

**Spanish Hospitals**

**Phase I-II MM ARI0002 (BCMA)**
- Production of CAR vector (Lentiv)
- CAR-T Production
- Biorreactor
- HCB
- CUN
- CAR-T infusion
- N=5

**EudraCT 2019-001472-11**

**HOSPITAL EXCEMPTIONS???
Pharma (vs Academic) CARTs

- Distance between hospital and manufacturing center.
- **High Price** / patient.
- After approval product maintained w/o changes: slow improvements.

- Academic CART proposals.
- New products by evolution of the knowledge.
- Few indications (no low frq TA).
- Accreditation: “Pharma” decides in some way

- Centralized approval (FDA, EMA, ...): responsible of homogeneity of product.
- Specificity and documentation in indication
- Central Approval: Easy to be accepted by the patient / family.

- Present limitations of other cancer therapies.
- To define allogenic products (universal CARTs).
- To stabilize the option of cellular immunotherapy.
3. Perspectives of using cutting-edge technologies in hospitals

- Options for “infrequent” targets (pediatric tumors, tTCR, etc).
- Faster development of new concepts/methods and tuning of consolidated concepts/methods.
- Economical sustainability (lower prices but direct reinvestment).
- Easier integration between clinicians and producers.
- Need of change of the key concept of autologous cell therapy as a drug -> new regulation ???
- Adjustments regarding microenvironment and other therapies in combination.
MINISTERIO
DE SANIDAD, CONSUMO Y
BIENESTAR SOCIAL

PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR

MULTIDISCIPLINARITY
Who is involved in ARI-0001 / CART19-BCN? (>175 professionals)
Thanks !!!