MOLMED

CAR-T Cells enter center stage !

COSTEM, Berlin, October 2017
Molmed sponsored symposium
»Approaches to potentially overcome CAR-T cell toxicity: anticytokine antibodies and suicide genes"

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SIRIC MARSEILLE CANCÉROLOGIE

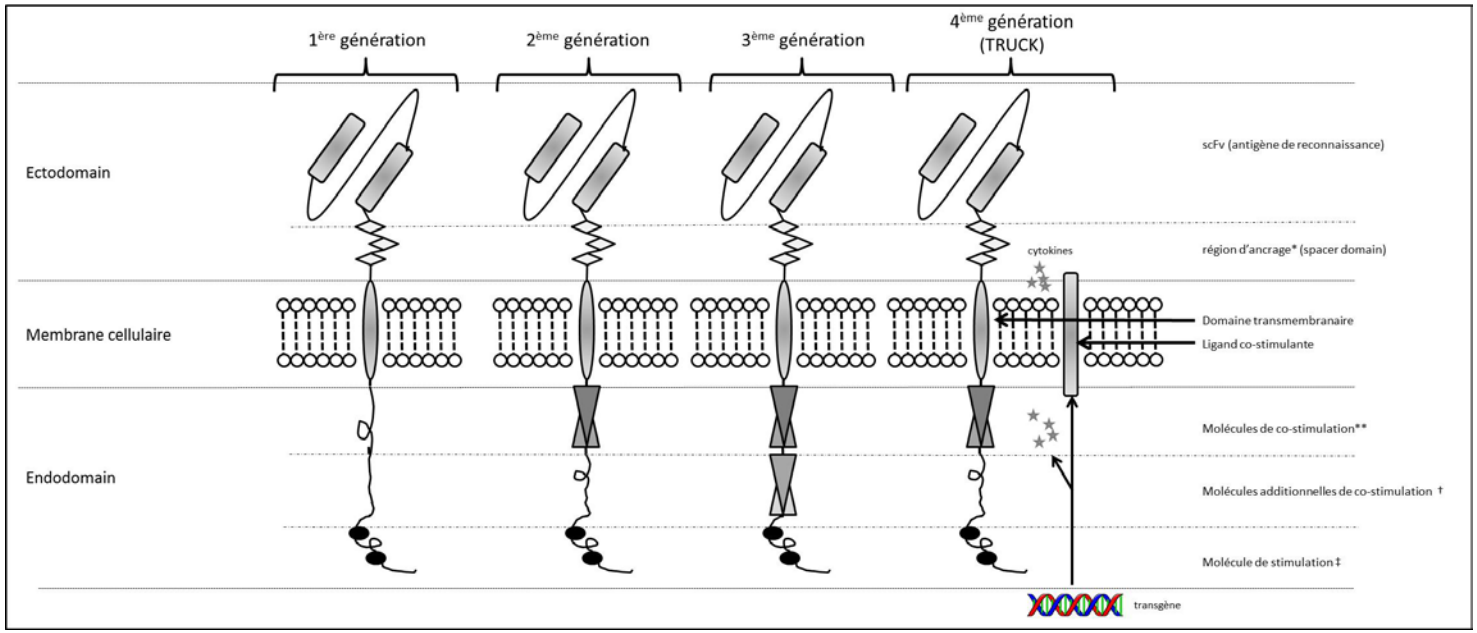
Disclosures

- **Molmed S.p.A:**
  - Hospitalities; co-investigator on protocol that evaluates Zalmoxis™ in the context of haplo-identical hematopoietic cell transplantation
- **Sanofi / Genzyme**
  - Consultancy; honorarium; hospitalities; research support
- **Novartis**
  - Hospitalities

Setting the stage

Gene Therapy Medicinal Products

- **Autologous or allogeneic T lymphocytes**
- **Gene modified ….**
  - retrovirus, lentivirus, non viral vector …
- **… to express a Chimeric Antigen Receptor (CAR)**
  - targeting an antigen expressed at the membrane of tumour cells
  - and possibly at the surface of some normal cells



Abbreviation: scFv: single chain variable fragment ; *généralement dérivé de IgG4 ou CD8 ; **Généralement CD28 ou 4-1BB ; † présents sur la troisième génération des CARs ; ‡généralement CD3ζ.

Yakoub-Agha et al, *Bull Cancer*, 2017, in press

Chimeric Antigen Receptor (CAR) T-Cell Therapy

CAR T-cell therapy uses the patient's own immune cells to personalize cancer immunotherapy.

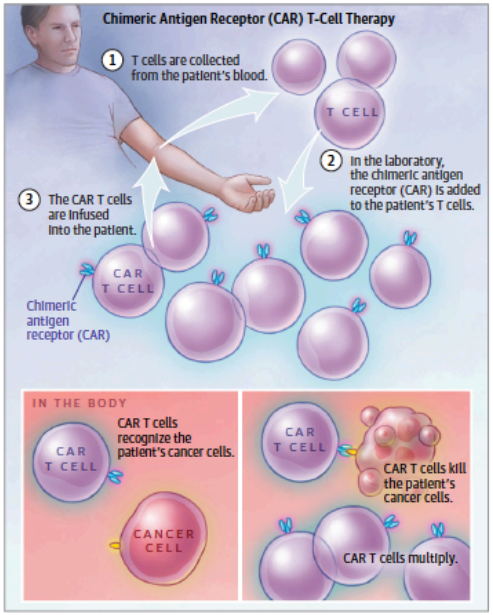
What Is CAR T-Cell Therapy?

CAR T-cell therapy is a cancer treatment that uses a patient's own immune system cells, called T cells, after these cells have been modified to better recognize and kill the patient's cancer. The T cells are engineered in the laboratory and then expanded to large numbers and infused back into the patient. This type of treatment transfers an immune system into the patient that is capable of immediately killing the cancer. CAR stands for *chimeric antigen receptor*, which represents the genetically engineered portion of the T cell. The CAR part of the T cell contains proteins that allow the T cells to recognize the specific cancer cells as well as become highly activated to kill the cancer cells.

Once in the body, the CAR T cells can further grow to large numbers, persist for long periods of time, and provide ongoing tumor control and possible protection against recurrence.

How Are CART Cells Made for Each Individual Patient and Administered?

The first step is to collect the patient's T cells from their blood using an outpatient procedure known as leukapheresis. These T cells are shipped to the laboratory for modification and manufacturing. The CAR-containing T cells are then returned for reinfusion into the patient. This process takes about 2 weeks. During the time that the cells are being developed, the patient will typically receive specific chemotherapy that can help prepare the immune system to support the CAR T cells once they are given back to the patient.



Possible Adverse Effects of CAR T-Cell Therapy

CAR T cells are administered in the hospital, where the patient can be monitored closely. Patients receiving CAR T-cell therapy typically develop temporarily low blood cell counts from the treatment, with fatigue, risk of infection, and need for transfusion support. Some patients may also have some of their normal immune cells, called B cells, destroyed as bystanders of the treatment, causing a condition called B-cell aplasia. Because B cells normally make antibodies to protect people from infections, people with B-cell aplasia need to have antibodies periodically given by vein.

In addition, there are 2 significant adverse effects that can occur after CAR T-cell therapy, both potentially serious: cytokine release syndrome (CRS) and neurologic complications. Patients with CRS typically develop a fever, rash, headache, and changes in blood pressure. The symptoms of neurologic toxic effects range from headaches to confusion, delirium, and seizures. Though the onset of the symptoms can occur within minutes or hours, they can be seen days to weeks later. The adverse effects are usually reversible, but rare cases of long-term symptoms have been noted. The possible long-term adverse effects may include cardiac dysfunction, bleeding, and kidney and/or liver failure. The management of severe CRS or neurotoxic effects may involve the use of specific drugs to reverse these symptoms.

Current Role

CAR T-cell therapy has received preliminary approval for treatment of children and young adults with a specific form of leukemia that has not been cured with initial chemotherapy treatment. It is being studied in many other cancer treatment settings and may become more widely used based on the results of ongoing clinical research.

For More Information

- *https://www.cancer.gov/about-cancer/treatment/research/car-t-cells*
- *https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy*

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Conflict of Interest Disclosures: None reported.
Section Editor: Howard (Jack) West, MD.

Kymriah™ and Yescarta™ are the first-of-their kind CAR-T Cell therapies to obtain a marketing authorization from the Food & Drug Administration (FDA)

- **Both medicinal products are autologous CAR-T cells targeting CD19**

- **Indications are different:**
  - ALL, below age 25 for Kymriah™
  - Poor-prognosis B cell NHL for Yescarta™

- **Both medicinal products are valued at high prices:**
  - US$ 475,000 for Kymriah™
  - US$ 377,000 for Yescarta™

Achievements and pitfalls

Achievements : CAR-T cells targeting CD19 have shown clinical efficacy for a variety of lymphoid malignancies

- Acute Lymphoblastic Leukemia (ALL)
- Advanced B-cell non-Hodgkin's lymphoma (NHL)
- Chronic Lymphocytic Leukemia (CLL)
- Multiple Myeloma

Achievements : CAR-T cells targeting BCMA have shown clinical efficacy in patients with multiple myeloma

- **Smaller groups of patients**
- **Suggest however that the risk benefit-ratio varies depending on the target and construct**

Novel immunotherapies in lymphoid malignancies

Connie Lee Batlevi[1], Eri Matsuki[1], Renier J. Brentjens[2] and Anas Younes[1]

Table 1 | Clinical efficacy of second generation CAR-T-cell therapy

Disease and treating institute	Number of patients	Conditioning therapy	Infused CAR T-cell dose	Response rate				Survival outcomes
				ORR (%)	CR (%)	PR (%)	SD (%)	
ALL								
MSKCC[44,48–50]	22 (16*+6‡)	CY (1.5–3.0 g/m²)	1–3 × 10⁶/kg	NA	91	NA	NA	Median OS: 9 months
UPenn[51]	30*	FLU (30 mg/m² × 4 days)/CY (500 mg/m² × 2 days): 13, FLU (30 mg/m² × 4 days)/CY (300 mg/m² × 2 days): 2, CY (440 mg/m² × 2 days)/VP (100 mg/m² × 2 days): 5, CVAD (CY 300 mg/m² q12h × 3 days, vincristine 2 mg day 3, doxorubicin 50 mg/m² day 3): 2, CY (300 mg/m² q12h × 3 days or 1,000 mg/m² × 1 day): 3, cloforabine 30 mg/m² × 5 days: 1; VP (150 mg/m² × 1 day)/Ara-C (300 mg/m² × 1 day): 1 None: 3	0.76–14.96 × 10⁶/kg	NA	90	NA	NA	NA
NCI[52]	20*	FLU (25 mg/m² × 3 days)/CY (900 mg/m² × 1 day)	1 or 3 × 10⁶/kg	NA	70	NA	15	RFS: 78.8% at 4.8 months
Fred Hutchinson[58]	7‡	Lymphodepleting chemotherapy	2 × 10⁵/kg, 2 × 10⁶/kg, or 2 × 10⁷/kg	NA	71.4	NA	NA	NA
CLL								
UPenn[45,60,61]	14 (3*+11‡)	FLU (30 mg/m² × 3 days)/CY (300 mg/m² × 3 days): 3, pentostatin/CY[§]: 5, bendamustine[§]: 6	0.14–5.9 × 10⁶	57.1	21.4	35.7	NA	NA
UPenn[62]	23‡	Lymphodepleting chemotherapy	5 × 10⁷ or 5 × 10⁸	39	22	17	NA	NA
NCI[63]	4*	FLU (25 mg/m² × 5 days)/CY (60 mg/kg × 2 days) + i.v. IL-2 following CAR-T-cell infusion	0.3–3 × 10⁷/kg	75	25	50	25	NA
NCI[64]	4*	FLU (25 mg/m² × 5 days)/CY (60 or 120 mg/kg × 2 days)	1–5 × 10⁶/kg	100	75	25	NA	NA
MSKCC[46,65]	10 (8*+2‡)	None: 4, CY-conditioning (1.5 or 3 g/m²): 4, BR (rituximab 375 mg/m² × 1 day, bendamustine 90 mg/m² × 2 days): 2	0.4–1.0 × 10⁷/kg	20	10	10	20	NA
MSKCC[49]	7‡	PCR[§] × 6 cycles, CY (600 mg/m²)	3–30 × 10⁶/kg	57.2	14.3	42.9	NR	NA
B-NHL								
NCI[63]	4*	FLU (25 mg/m² × 5 days)/CY (60 mg/kg × 2 days) + i.v. IL-2 following CAR-T cell infusion	0.3–3 × 10⁷/kg	100	0	100	0	NA
NCI[64]	11*	FLU (25 mg/m² × 5 days)/CY (60 or 120 mg/kg × 2 days)	1–5 × 10⁶/kg	88.9	55.6	33.3	11.1	NA
NCI[66]	9‡	FLU (30 mg/m² × 3 days)/CY (300 mg/m² × 3 days)	1 × 10⁸/kg	66.7	11.1	55.6	0	NA
MSKCC[67]	6‡	BEAM conditioning and autologous SCT	5–10 × 10⁶/kg	100	100	0	0	NA
UPenn[68]	8‡	EPOCH, CY, bendamustine, FLU/CY[§]	3.7–8.9 × 10⁶/kg (median 5.8 × 10⁶/kg)	50	37.5	12.5	0	NA
Fred Hutchinson[58]	9‡	Lymphodepleting chemotherapy	2 × 10⁵/kg, 2 × 10⁶/kg, or 2 × 10⁷/kg	66.7	11.1	55.6	NA	NA

*In published report. ‡In reported abstract. §Doses unknown. ||PCR is pentostatin 4 mg/m² day 1, cyclophosphamide 600 mg/m² day 1, rituximab 375 mg/m² day 1. Abbreviations: ALL, acute lymphocytic leukaemia; BEAM, BCNU (carmustine) + etoposide + cytarabine + melphalan; B-NHL, B-cell non-Hodgkin lymphoma; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CR, complete response; CVAD, cyclophosphamide + vincristine + doxorubicin + dexamethasone; CY, cyclophosphamide; EPOCH, etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone; FLU, fludarabine; Fred Hutchinson, Fred Hutchinson Cancer Research Center; i.v., intravenous; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NA, not applicable; ORR, overall response rate; OS, overall survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; UPenn, University of Pennsylvania; VP, etoposide.

Hurdles : CAR-T cells targeting CD19 can trigger severe side-effects

- **Cytokine Release Syndrome (CRS)**
- **CAR-T-cell-related encephalopathy syndrome (CRES)**
- **Request a tight organization for prompt diagnosis and management**

REVIEWS

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4], Cristina Gutierrez[5], Frederick L. Locke[6], Krishna V. Komanduri[7], Yi Lin[8], Nitin Jain[4], Naval Daver[4], Jason Westin[1], Alison M. Gulbis[9], Monica E. Loghin[2], John F. de Groot[2], Sherry Adkins[1], Suzanne E. Davis[10], Katayoun Rezvani[3], Patrick Hwu[10],

Hurdles: implementing new organizations to deliver hematopoietic cellular therapies

- **Public – private partnership or innovative hospital – industry partnership to produce CAR-T Cells**
- **Partnership between cell processing facilities and hospital pharmacies for the delivery and administration of CAR-T Cells**
- **Tight collaboration between hematologists and intensive care practitioners to allow for early diagnosis and immediate management of complications**

Hurdles: can CAR-Cell therapies be effective in oncology, beyond CD19+ hematological malignancies

- **Other hematological malignancies:**
  - AML, MDS
  - others

- **Solid tumors**
  - Target antigens expressed on epithelial cells
    - Off-target effects
  - Accessibility of tumor sites to CAR-T Cells

Hurdles: overcoming financial toxicities

- **CAR-T Cells impersonate personalized medicine**
- **Are CAR-T Cells production and delivery financially sustainable in the context of industrial and centralized manufacturing organizations?**
  - Alternative: “point-of-care” (POC) production?
- **Need for new payment models ?**
  - “Pay-per-cure” ?
  - Pricing commensurate with savings in other health expenditures ?

Will CAR-T Cells represent one of the first commercial successes of a cellular therapy / an ATMP ?

Medicinal products that qualify as ATMPs, and have received marketing authorization from EMA or FDA

Filing			
2007	**ChondroCelect**	Tigenix	▪ Cartilage defects of the knee
	Contusugene	Introgene	▪ Carcinoma of the head and neck
2009	**Cerepro**	Ark Ther.	▪ Glioma
2010	**Glybera**	UniQure	▪ Lipoprotein lipase deficiency
	Caomecs/OraNera	CellSeed	▪ Limbal stem cell deficiency
2011	**MACI**	Vericel	▪ Cartilage defects of the knee
	Provenge	Dendreon	▪ Prostate Cancer
	Holoclar	Chiesi	▪ Limbal stem cell deficiency
2013	**Heparesc**	Cytonet	▪ Urea cycle disorders
2014	**Zalmoxis®**	MolMed	▪ High risk haematological malignancies
	Imlygic	Amgen	▪ Unresectable melanoma
2015	**Strimvelis™**	GSK	▪ ADA-SCID
2017	**Kymriah™**	Novartis	▪ Relapsed or refractory ALL
2017	**Yescarta™**	Gilead (Kite)	▪ Relapsed or refractory NHL

What’s going on in Europe ?

Europe is lagging behind north-America and Asia in terms of preclinical and clinical activity in the field

Review

EMBO Molecular Medicine

Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts

Jessica Hartmann[1,*], Martina Schüßler-Lenz[2,3], Attilio Bondanza[4] & Christian J Buchholz[1,3,**]

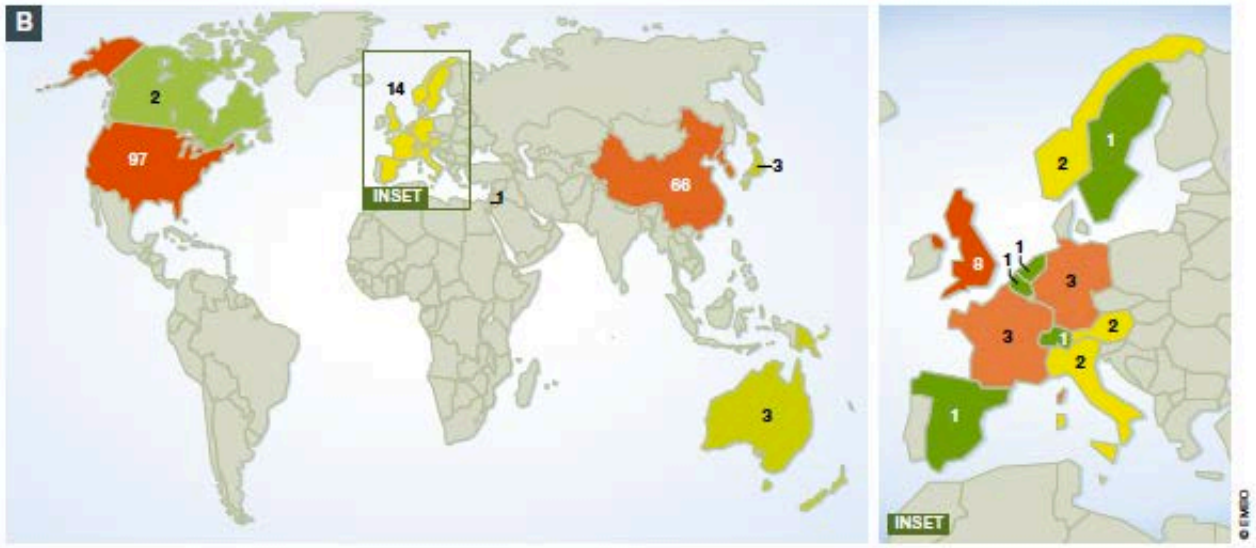

Figure 2. CAR T cell trials over time and geographical distribution.

(A) Timeline of cancer CART cell trials as listed in Datasets EV1 and EV2 distinguishing between ongoing number (dark blue bars) and newly initiated trials in the indicated year (light blue bars). (B) Geographical distribution of worldwide ongoing CAR T cells clinical trials (left) and distribution of trial sites of the ongoing European studies (right). Five studies are multi-centric, of which four are multi-country trials in Europe (Dataset EV5). Long-term follow-up studies are not included. Color code indicates the prevalence of trials from low (green) to high (red).

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First Announcement

2nd CTIWP Scientific Symposium

SAVE THE DATE!

January 18th-20th 2018

Corpus Congress Centre
Leiden, Netherlands

Local and CTIWP organizing committee:

Gerard Bos, Lotte Wieten, Fred Falkenburg, Jürgen Kubal, Chiara Bonini and Christian Chabannon.

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