CAR-T cells
et
Leucémies aigues lymphoblastiques de l'enfant, de l'adolescent et du jeune adulte

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Liens d’intérêt

- Novartis, Servier, Celgene
- Jazz, Shire
- Janssen, Sanofi
- Amgen

- Grants: Shire/Servier

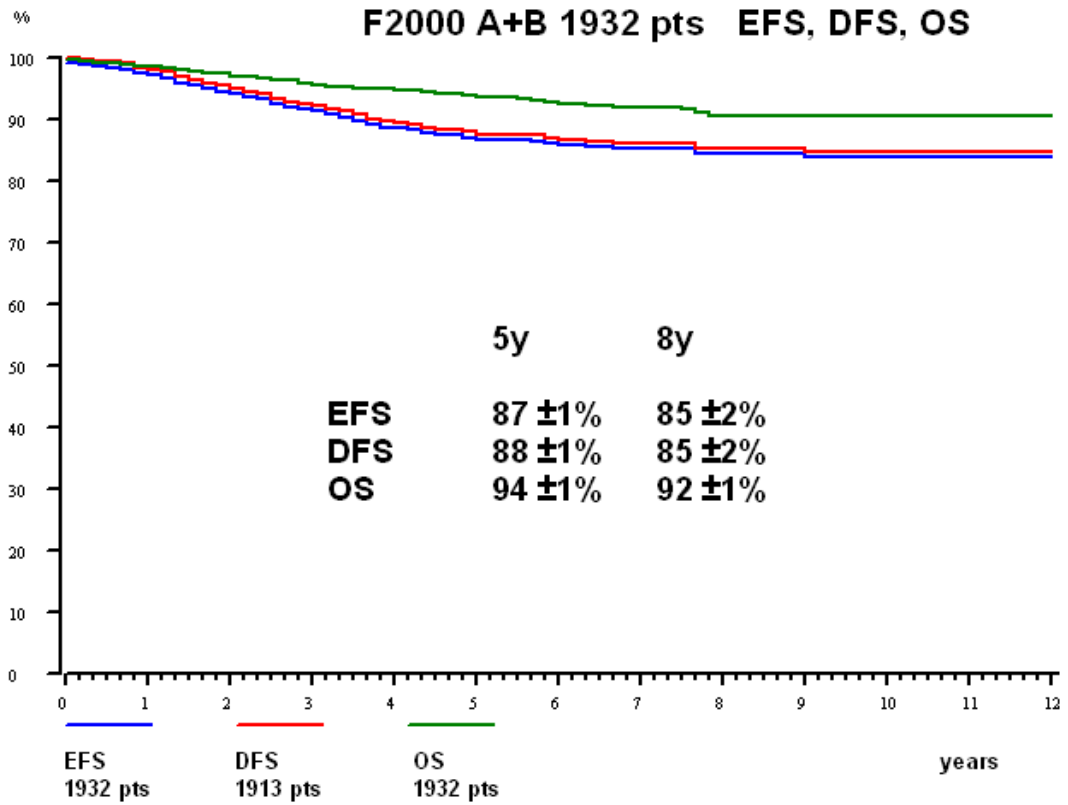
Childhood and adolescent ALL in FRANCE

Overall Results B+T ALL

	Event-Free Survival		Overall Survival	
	5 years	8 years	5 years	8 years
FRALLE 2000 (2146 pts)	84.0%	82%	91%	89%
EORTC 58951 (1947pts)	82.6%,	81.3%	89.7%	88.1%

Results FRALLE 2000 B-ALL

(non Philadelphia & >12month-old)



Leucémies aiguës lymphoblastiques : problèmes persistants

Efficacité:

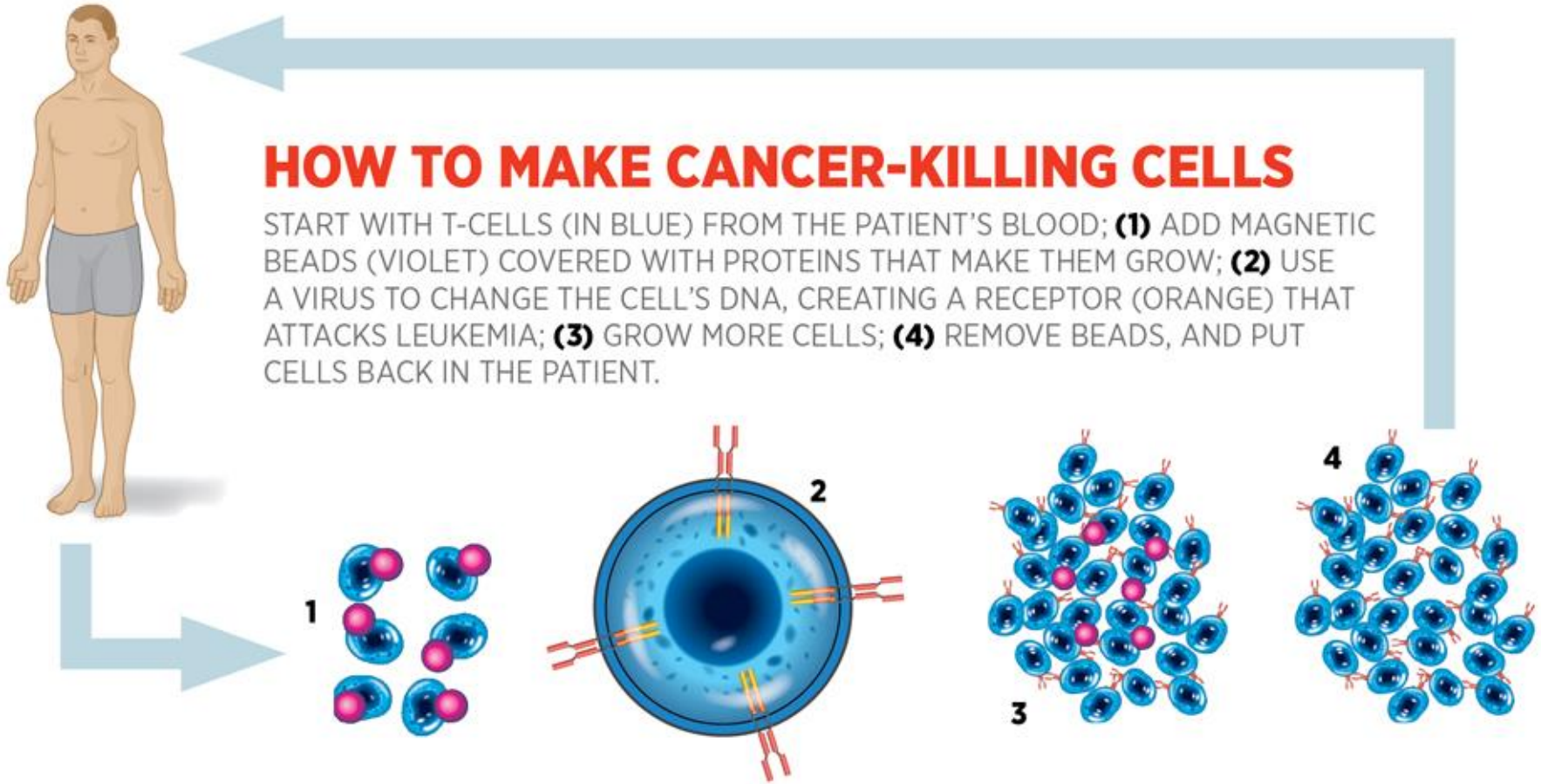
Toujours des rechutes!

- 15% chez les enfants
- beaucoup plus chez les nourrissons (35 à 40%) les adolescents (25%) les adultes (35% et plus)
- certaines rechutes sont quasi incurables: t (1; 19), t (17; 19), hypodiploïdie, p53 mut, LAL-T

Globalement: pronostic insatisfaisant des patients LAL en rechute

Toxicité:

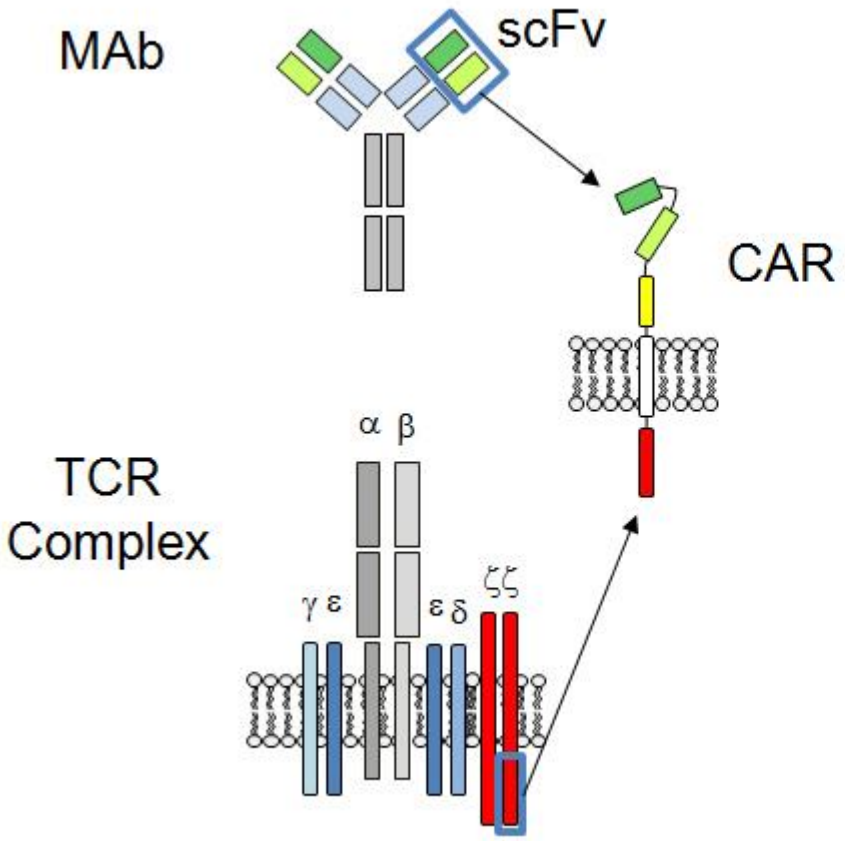
- Décès non leucémiques: décès en induction; et décès en RC
- Traitement prolongé avec immunosuppression et nombreux effets indésirables (EI) souvent graves (EIG) liés au traitement
- Plus la thérapie est intensive et longue, plus les EI et EIG augmentent
- Le plus toxique : greffe de CSH en CR1 ou plus (GVHD, EI liés à ICT, etc.)

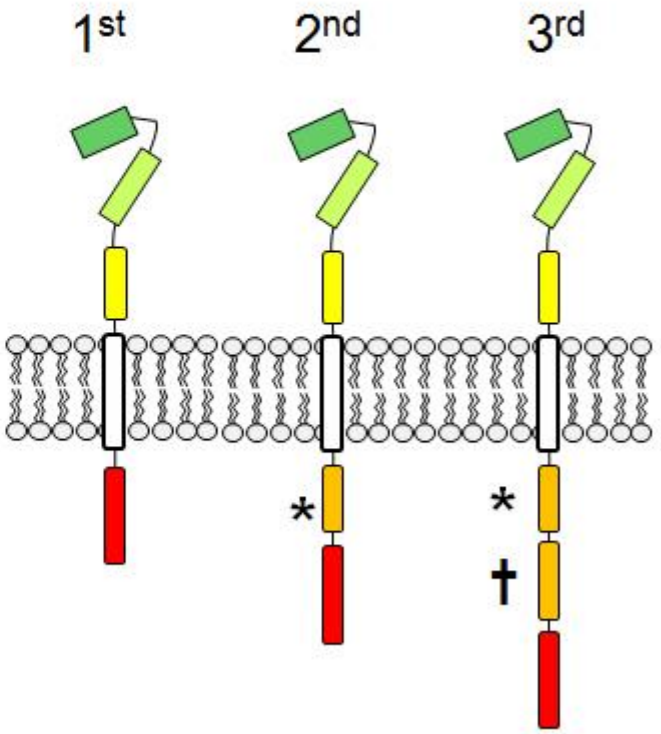


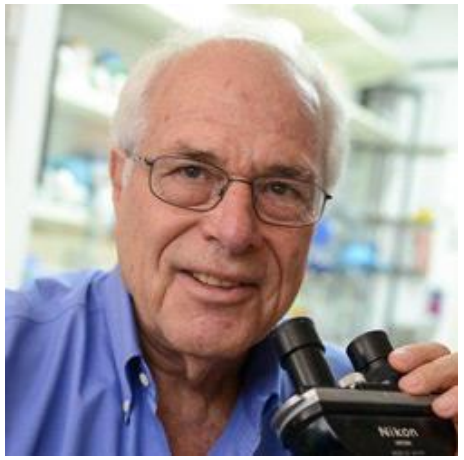
Is This How We'll Cure Cancer?

This story appears in the May 26, 2014 issue of Forbes.

Chimeric antigen receptor (CAR)

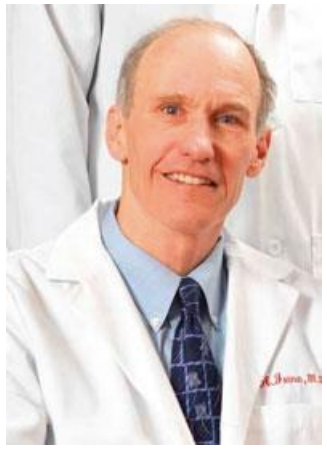






Zelig Eshhar

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity
Gross G, Waks T, **Eshhar Z.**
Proc Natl Acad Sci USA 1989 Dec;86(24):10024-8.



Carl June

Sci Transl Med 2011 Aug 10;3(95):95ra73.
T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia.
Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, **June CH**

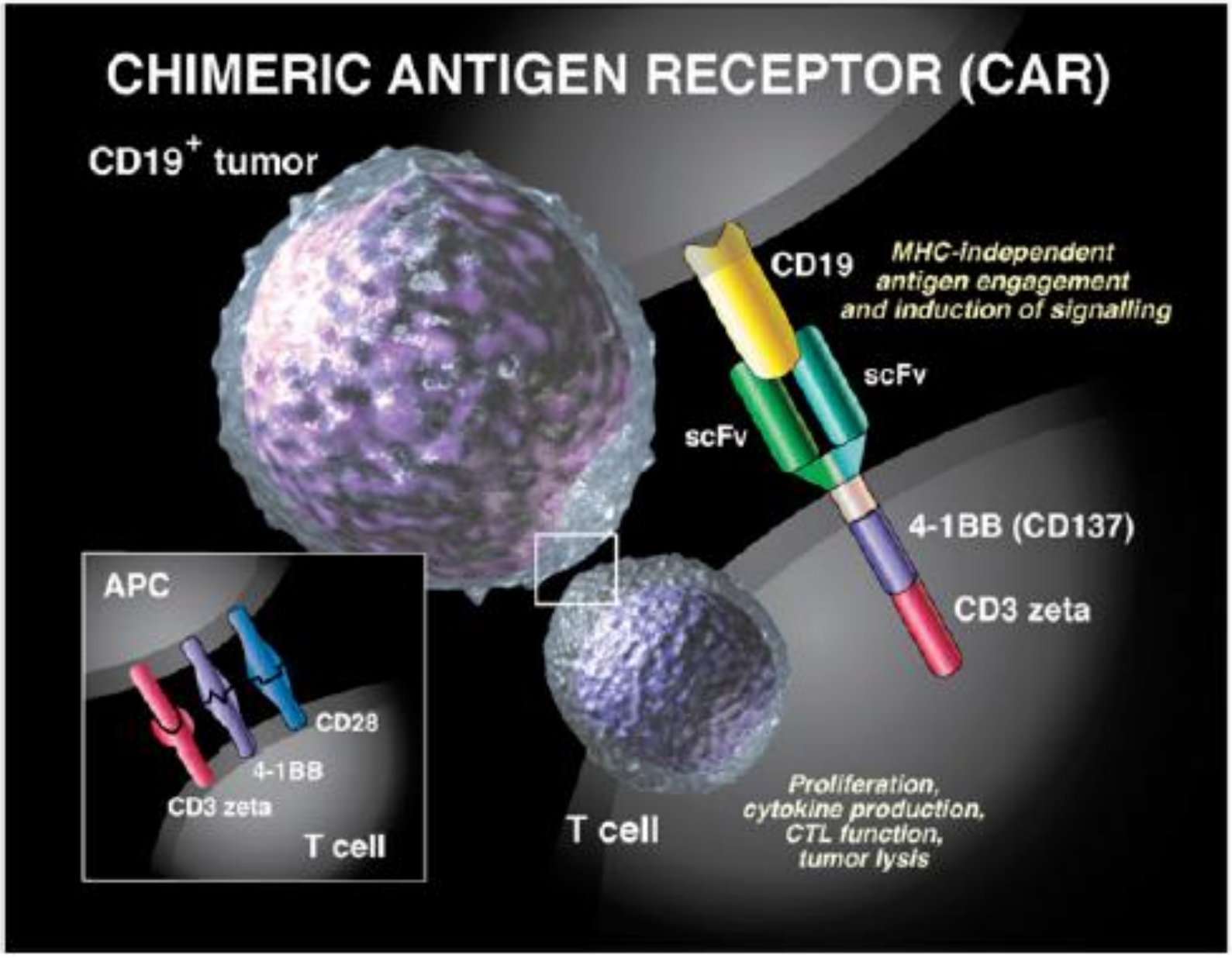
Dario Campana

Leukemia 2004 Apr;18(4):676-84.
Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia.
Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL, **Campana D**

Steve Grupp

Chimeric antigen receptor-modified T cells for acute lymphoid leukemia.
Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH.
N Engl J Med 2013 Apr 18;368(16):1509-1518.

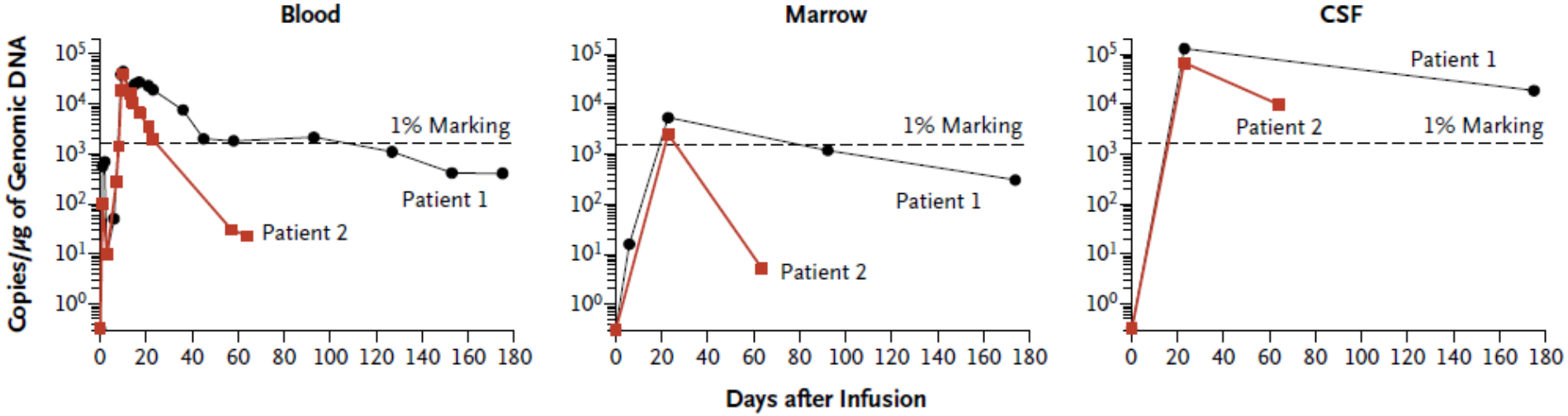
CD 19 l'antigène idéal?



Barrett et al, Curr Opinion Pediatr 2014

CTL019 CAR-T cells et LAL de l'enfant : les premiers cas

The New York Times



-100 to 100,000 times in vivo proliferation

- durable antitumor activity and prolonged persistence in patients with B-cell tumors, including 1 sustained CR in a patient with ALL.

Grupp S et al, NEJM 2013

Autologous CD19 CAR-T in R/R B-ALL
Phase 1/2 studies

Study	Population	CD19-CAR	V	N	Cond.	T-cells	ORR
Maude, 2013[1]	Ped+adult	4-1BB	LV	30	CyF	unselected	90%
Lee, 2015[2]	Ped+YA	CD28	gRV	21	Cy	unselected	68%
Gardner, 2017[3]	Ped+YA	4-1BB	LV	45	CyF	1:1 CD4/8	93%
Maude, 2018[4]	Ped+YA	4-1BB	LV	75	CyF	unselected	81%
Park, 2018[5]	Adult	CD28	gRV	53	Cy/CyF	unselected	83%
Hay, 2019[6]	Adult	4-1BB	LV	53	Cy/CyF	1:1 CD4/8	85%

Cy, cyclophosphamide; CyF, cyclophosphamide + fludarabine; Ped, paediatric; YA, young adults;
LV, lentivirus; gRV, gamma-retrovirus; Auto, autologous.

1. Maude SL, et al. N Engl J Med 2014;371:1507–17;
2. Lee DW, et al. Lancet 2015;385:517–28;
3. Gardner RA, et al. Blood 2017;129:3322–31;
4. Maude SL, et al. N Engl J Med 2018;378:439–48;
5. Park JH, et al. N Engl J Med 2018;378:449–59;
6. Hay KA, et al. Blood 2019; doi: 10.1182/blood-2018-11-883710 [Epub].

Différences selon les essais/ compagnies / littérature

FABRICATION DES CELLULES CAR-T

- méthodes de transduction
  - Lentivirus ou Rétrovirus
  - « Sleeping beauty transposon/transposase» (plasmides, ADN «minicircles»)
  - électroporation d'ARNm
- deuxième vs troisième génération vs « armé »
- domaines de costimulation: 4-1BB vs CD28 / persistance et rechute
- monospécifique vs bispécifique

LYMPHODEPLETION

- cyclophosphamide (Cy) vs Fludarabine-Cy, dosage de chaque composant

COMPOSITION DU « MEDICAMENT » INJECTE

- nombre de cellules CAR-T injectées
- composition: balance exacte CD4 / CD8…
- CAR-T cells autologues vs allogéniques (« gene editing »)

TRAITEMENT POST CAR : HSCT OU NON

ACADEMIE OU INDUSTRIE

SYNDROME DE RELARGAGE DES CYTOKINES et NEUROTOXICITE vers un consensus?

Biol Blood Marrow Transplant ■■ (2018) ■■■–■■■

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[2], Elena Mead[2], Steven Pavletic[6], William Y. Go[8], Lamis Eldjerou[9], Rebecca A. Gardner[10], Noelle Frey[11], Kevin J. Curran[2], Karl Peggs[12], Marcelo Pasquini[13], John F. DiPersio[4], Marcel R.M. van den Brink[2], Krishna V. Komanduri[14], Stephan A. Grupp[15,*], Sattva S. Neelapu[16,**]

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[16] *The University of Texas M.D. Anderson Cancer Center, Houston, Texas*

CRS : définition proposée (consensus de l'ASBMT)

"a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.

Symptoms can be progressive, **must** include **fever** at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."

Lee D et al, BBMT 2018

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- may manifest as
  - delirium, encephalopathy,
  - aphasia,
  - lethargy, difficulty concentrating, agitation,
  - tremor, seizures,
  - and, rarely, cerebral edema.
- In addition, headache is very common (might not represent neurotoxicity per se)

Lee D et al, BBMT 2018

CRS and neurotoxicity in CD19 CAR-T ALL studies

Study	CD19-CAR	N	Population	CR	CRS	Neurotoxicity/CRES
Maude, 2013[1]	4-1BB	30	Ped+Adult	90%	**100% 27% severe**	**43% encephalopathy, seizure, aphasia**
Lee, 2015[2]	CD28	21	Ped+YA	68%	**76% 28% severe**	**29% encephalopathy, hallucination**
Gardner, 2017[3]	4-1BB	45	Ped+YA	93%	**93% 23% severe**	**49% 21% severe**
Maude, 2018[4]	4-1BB	75	Ped+YA	81%	**77% 46% severe**	**40% 13% severe**
Park, 2018[5]	CD28	53	Adult	83%	**85% 26% severe**	**43% 42% severe**
Hay, 2019[6]	4-1BB	53	Adult	85%	**75% 19% severe**	**23% severe**

1. Maude SL, et al. N Engl J Med 2014;371:1507–17;
2. Lee DW, et al. Lancet 2015;385:517–28;
3. Gardner RA, et al. Blood 2017;129:3322–31;
4. Maude SL, et al. N Engl J Med 2018;378:439–48;
5. Park JH, et al. N Engl J Med 2018;378:449–59;
6. Hay KA, et al. Blood 2019; doi: 10.1182/blood-2018-11-883710 [Epub].

Robert Debré experience with Tisagenlecleucel at 13.02.19

Only pediatric center opened in France until January 2019

Frame

- Clinical trials
- Named patient basis (Temporary Use Authorization) (ATU)
- Cohort ATU
  - Authorization of the center for use : ANSM (French Regulatory Agency)
  - Accreditation of the center by Novartis (apheresis ++)
  - Each administration to be OK'd by Novartis
  - paying precommercial use : 320 kE

Characteristics of the 16 infused pts

B-ALL GENETICS

- TEL-AML1 : 6
- Hyperdiploidy : 3
- iAMP21 : 1
- BCR-ABL : 3
- BCR-ABL like : 1
- B-Other : 2 (IKZF1 del:1)

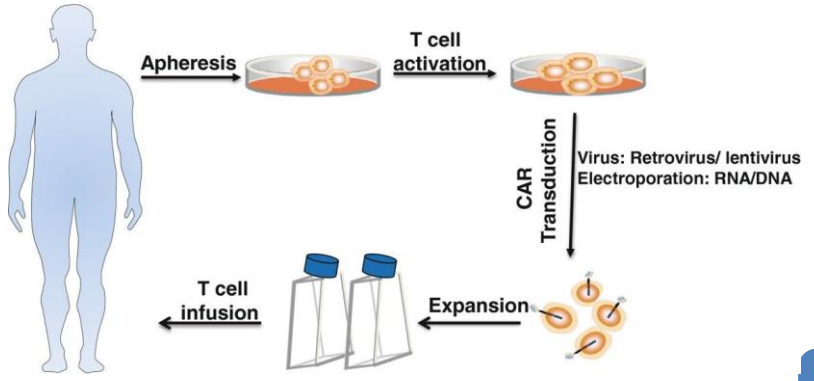
Prior HSCT : 12/16 **(75%)**

Leukemia features at apheresis

- 1st **refractory** relapse : 5
- 2nd relapse: 1
- 2nd **refractory** relapse : 5
- 3nd relapse: 1
- 4th **refractory** relapse : 2
- 5th relapse (CNS) : 1
- 1st Isolated extramed (BM MRD neg):1

Leukemia prior to lymphodepletion

- Marrow Blasts ≥ 5% (5-96) : **8**
- Marrow Blasts < 5% : **8**
  - MRD > 10^{-2}: 1
  - 10^{-4} <MRD < 10^{-2}: 0
  - MRD + < 10^{-4} : 4
  - MRD undetectable :1
  - MRD UK: 2



Apheresis N = 25

Between 05 april 2016 and 13 february 2019

*Median age = **10,2 years** (0,8 -16)*

Intention to treat patients N = 20

Not infused N = 2

Disease progression = 1

Infection-related death = 1

Waiting N = 2

Infusion planned in february 2019

Infused patients N = 16

Between 30 june 2016 and 15 january 2019

CRS (grade3) N = 6

Neurological events N = 5

ICU = 6

Death = 0

Molecular / CMF or morphological Relapse N = 4

CD19+ = 2 ; CD19- = 2

Deceased N = 1

Alive in complete remission N = 12

Median follow up = 13,2 months (1 -32)

Updated on 13 FEB 19

Rechute après CARs ?

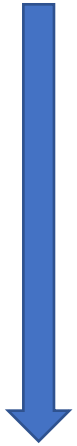
- Rechute CD19(+)
- Rechute CD19(-) (~60-80% des rechutes)
  - down regulation
  - Délétion du gène, mutations, alternative splicing
- Changement de lignage (LAL vers LAM!)
  - MLL++
  - ZNF384

La plupart de ces événements se passent la première année

Sotillo E et al, Cancer Discovery 2015;
Gardner R et al, Blood 2016;
Jacoby E et al, Nature Com 2016
Oberley MJ et al, Pediatr Blood & Cancer 2018

Concepts possibles dans un futur proche pour les LAL-B

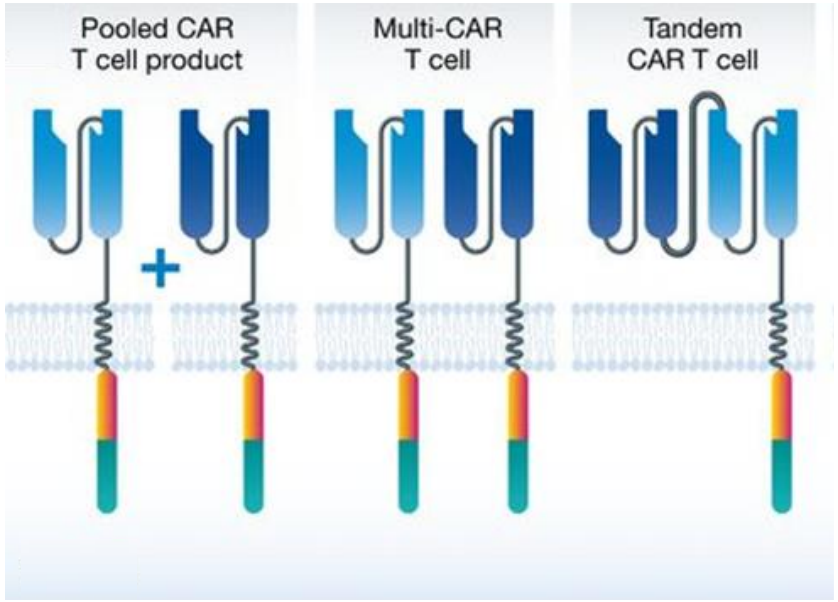
- Remplacement de l'allogreffe par les CARs autologues persistants:
  - Advanced disease (relapse >= 2, relapse post HSCT)
  - 1st high-risk relapse
  - 1st line very-high Risk ALL (non responding to chemo)
  - 1st line HR ALL (replacement of prolonged intensive chemo?)



time

- CARs allogéniques : plus un pont vers la greffe sauf si des injections répétées sont possibles après des chimiothérapies de lymphodéplétion plus légères

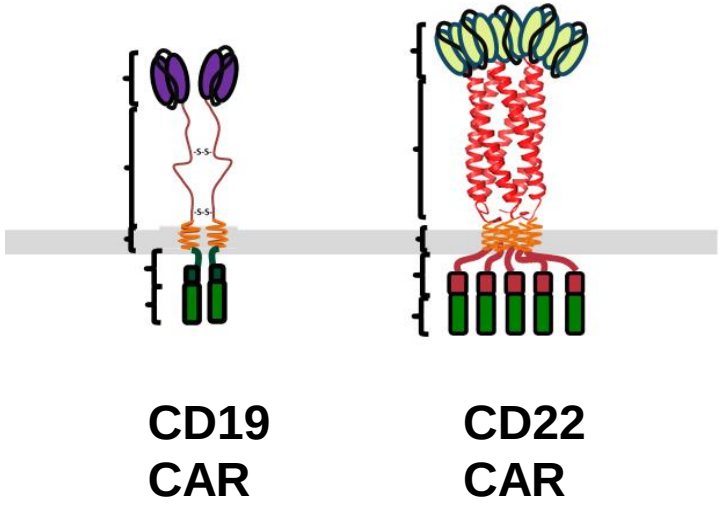
Next generation CAR-T



Hartmann J, et al. EMBO Mol Med 2017;9:1183–97.

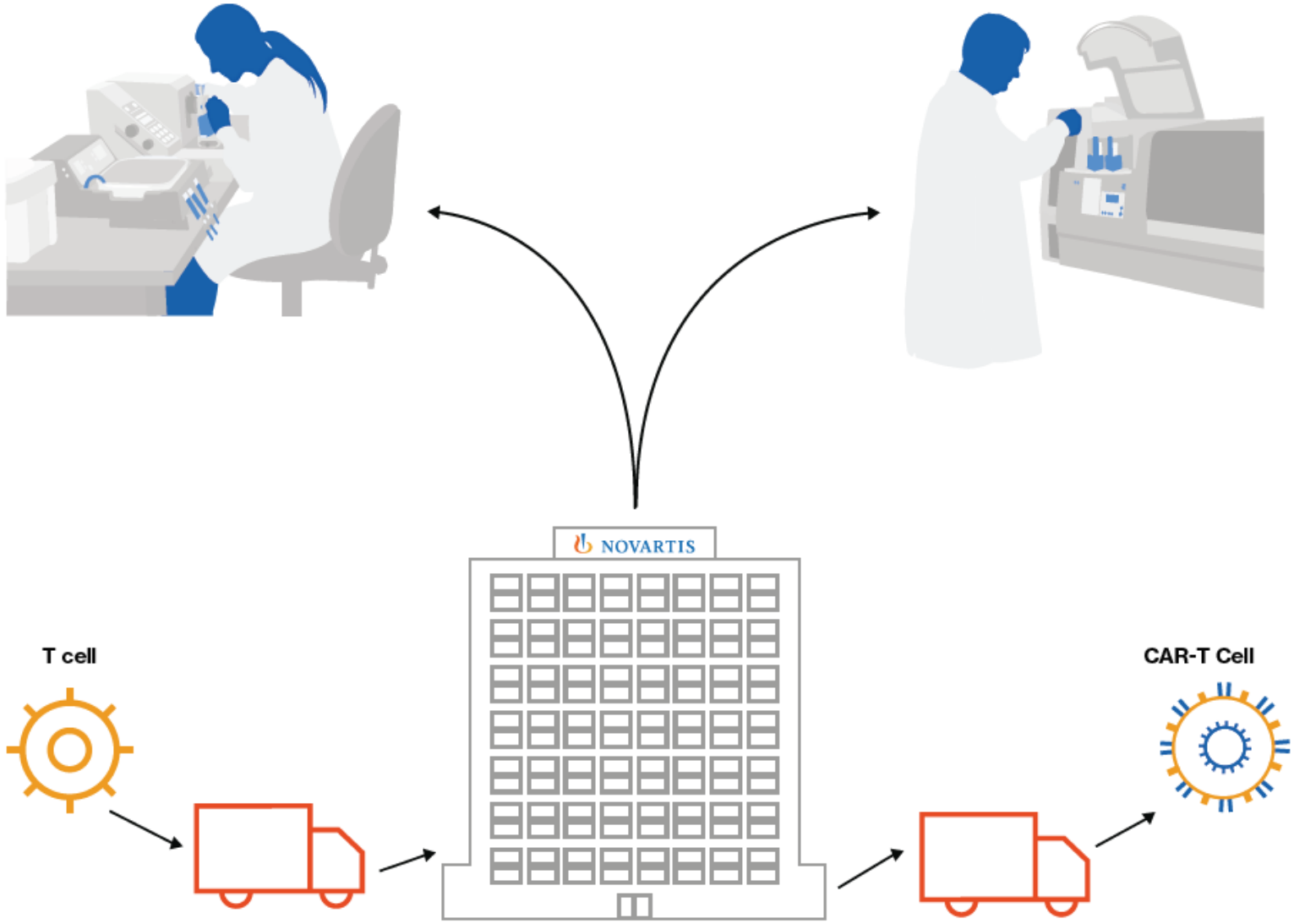
Example of a bispeficic CAR

- Ground : AMELIA Phase 1 preliminary data
  - ASH 2018 Amrolia P et al :
    - 10 pts
    - 6/6 CR : at 3x 10^6 cells or more/kg and persistence
    - low toxicity, no C19-/CD22- relapse
    - Efficacy and dose escalation ongoing
- AMELIA Phase II Trial
- **AUTOLUS Bispecific CAR (CD19/CD22)**
- For pts with B-ALL and MRD TP1 > 5% or t(17;19)
- Availability?



2 points de réalité

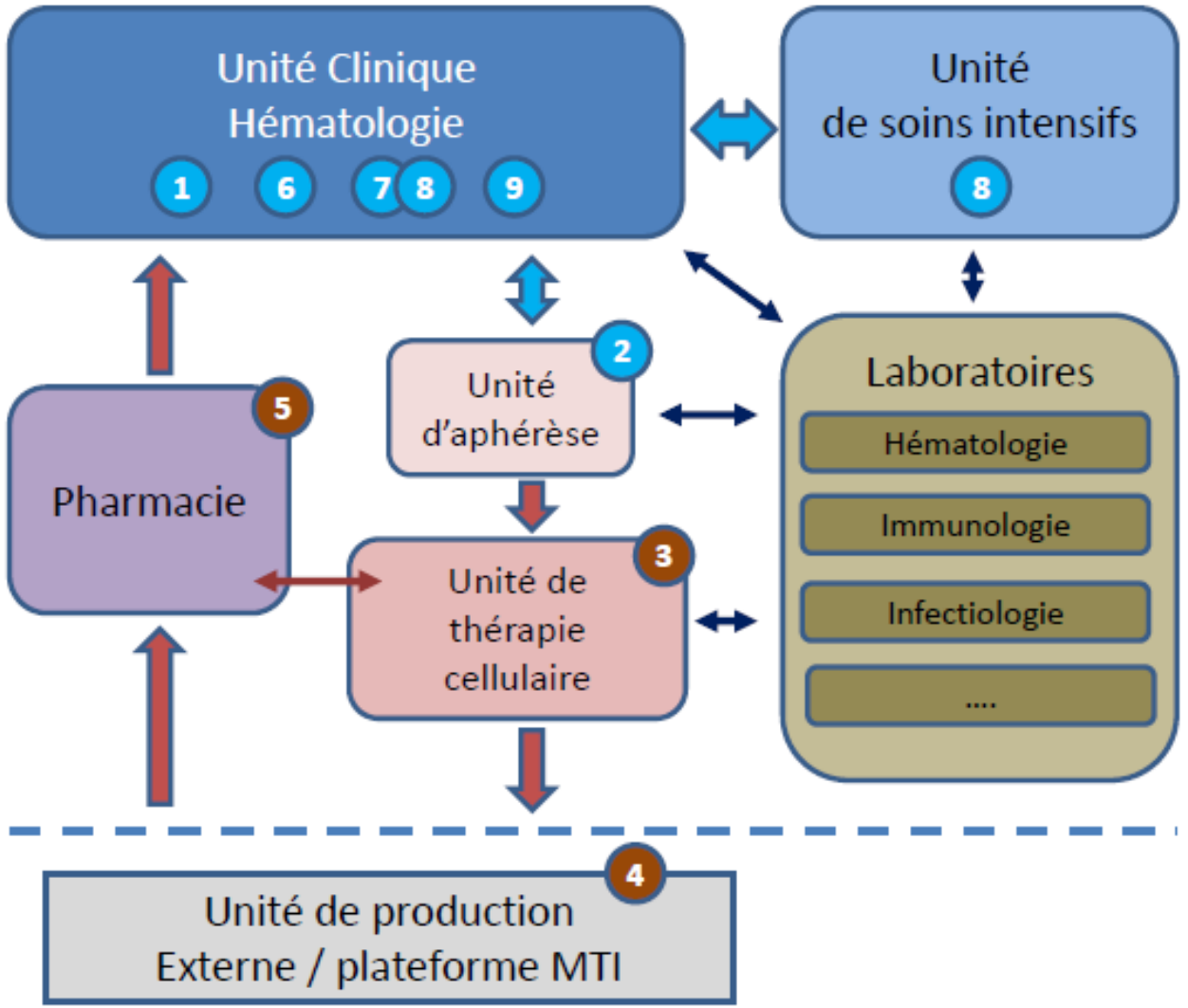
- Complexité
- « toxicité financière »



EST-CE SI SIMPLE?

Complexité ++ du parcours des cellules et du patient

1. Screening n°1
2. Aphérèse
3. Conservation du produit d'aphérèse
4. Production
5. Réception du médicament (OGM)
6. Screening n°2
7. Lymphodéplétion / injection
8. Gestion des EI court terme
9. Gestion des EI long terme (OGM…)



Tisagenleucleucel et LAL
AMM Européenne: août 2018
ATU de cohorte: fin le 24 Mars 2019

- âge < 26 ans et porteur d'une LAL-B
- 2ème rechute ou Réfractaire après deux lignes

  ou 1ère rechute post greffe
  - à noter 3 indications de fait autorisées alors que pas de data

    RECHUTES EXTRA-MEDULLAIRE, AGE < 3 ANS, PRE-EXPOSITION AU BLINATUMOMAB
- 320.000 E HT; prix final en attente (ASMR3)
- 2 centres (RDB SLS): extension en cours
- critères d'autorisation publiés (JORF n°0085 du 10 avril 2019)

1ère enfant traitée en France: fille de 11 ans

- Avril 2010: LAL de la lignée B TEL-AML1 + diagnostiquée chez une fille de 5 ans
- Sept 2013: Rechute médullaire
- Décembre 2013: Allogreffe géno-identique en 2ème RC
- Nov 2014: rechute moléculaire / 3 injections de Lymphocytes du donneur: échec
- Mai 2015: rechute avérée
  - Nombreuses chimiothérapies, y compris la clofarabine et le moxétumomab
  - Phase palliative
- *30 mars 2016: INCLUSION **ELIANA TRIAL** ; 5 avril: aphérèse*
- *30 juin 2016: injection de CTL019 après lymphodéplétion*
- *J3: CRS de grade 3; Soins intensifs (fluides, vasopresseurs); Tocilizumab: apyrexie à H4*
- *J28: Rémission complète avec Maladie Résiduelle indétectable*
- *2 septembre 2016: retour à l'école*
- *M3: RC persistante (MRD neg); aplasie des cellules B.*
- *M10: a gravi une montagne de 3000 m*
- *M34: Va bien. Aplasie des cellules B persistante*

CONCLUSION

- Une révolution!

- Nombreux problèmes soulevés
  - Scientifiques
  - Technologiques
  - Médicaux
  - Economiques
  - Ethiques

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