

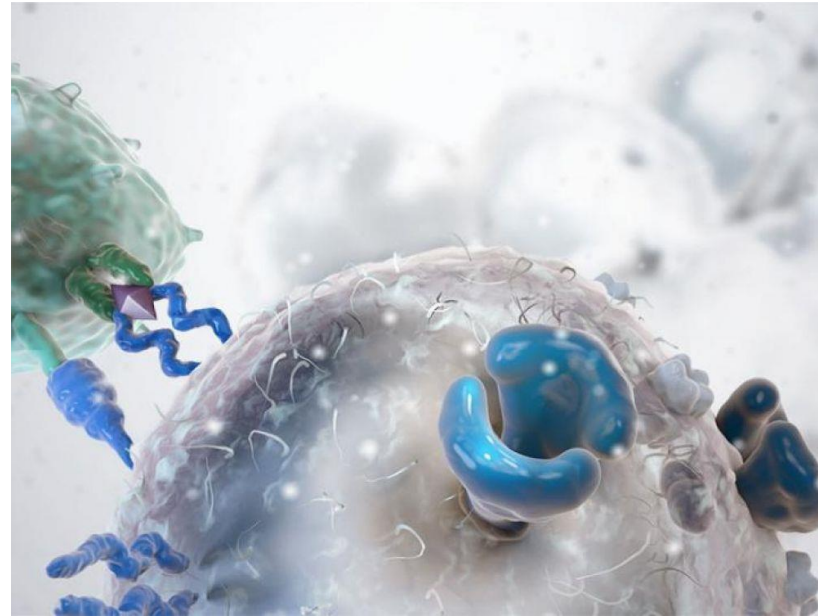
L'histoire des CAR-T...



Right

UNITÉ DE RECHERCHE EN SANTÉ

UNIVERSITÉ DE
FRANCHE-COMTÉ



Collège d'hématologie des Hôpitaux généraux Strasbourg 06-07 avril

Maxime Fredon (PhD Student)

UMR1098-RIGHT/ EFS Bourgogne Franche-Comté / Université de Franche Comté

Team : Therapeutic Innovation in Cancer Immunology (TICI)

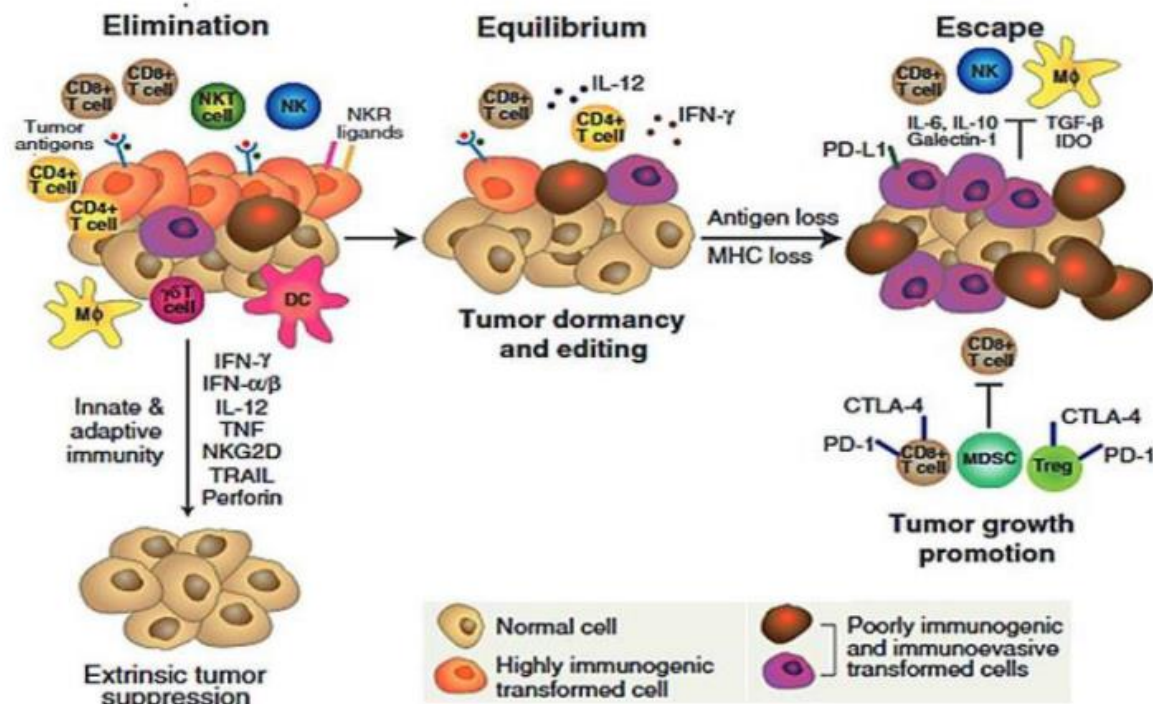
Pr Francine GARNACHE OTTOU
UMR1098-UFC-EFS BFC- Laboratoire
Hématologie CHU Besançon



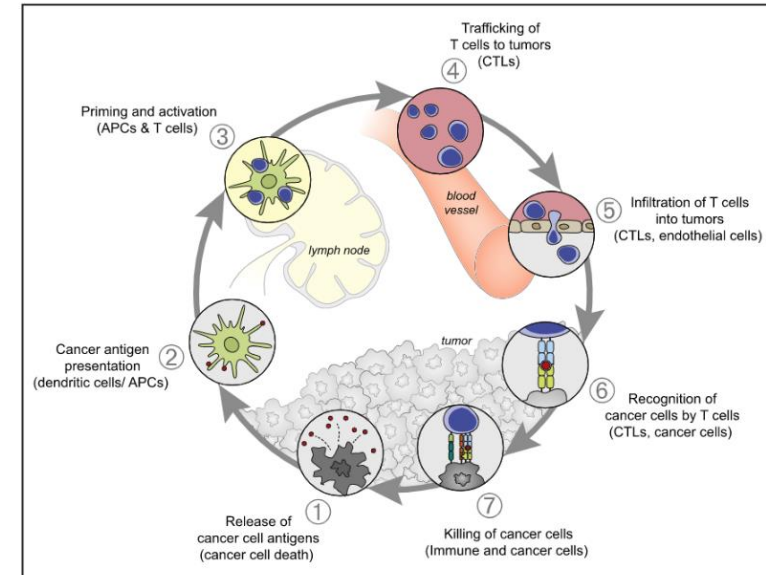
Rôle du système immunitaire en cancérologie

The Cancer-Immunity cycle : immunosurveillance

Cancer Immunoediting : the three E

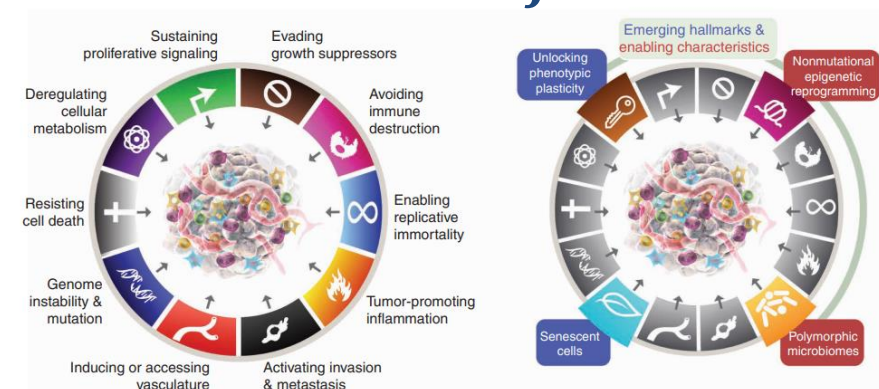


Dunn, G.P et al., *Nat Immunol* 2002
Schreiber R,B et al., *Science*, 2011



Chen, D.S and Mellman, I., *Immunity*, 2013

Hallmark of cancer



Hanahan, D and Weinber, R.A., *Cell*, 2000
Hanahan, D., *Cancer Discovery*, 2022

L'immunothérapie des cancers



Pr Zélig Eshhar
Dudley et al., Science 2002

(Schwartzentruber DJ et al., NEJM 2011)

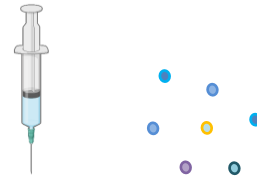
(Adotévi et al., JCO, 2022)

Eduquer

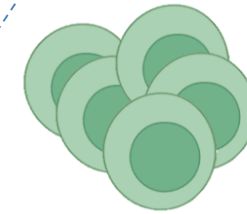
Le système immunitaire

Immunothérapie active

Vaccins
(UCP Vax)



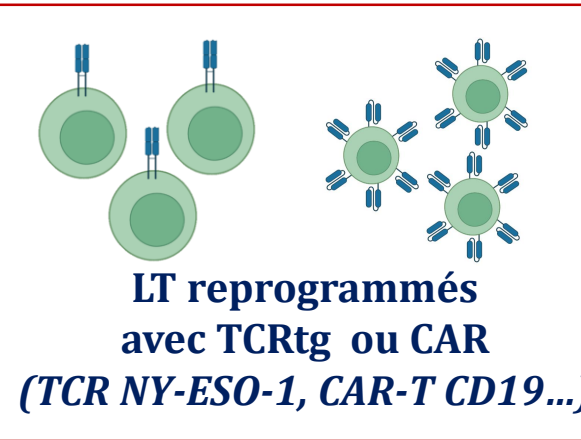
Cytokines
(IL-2, IFN- γ)



TIL

Stimuler
une réponse immunitaire

Thérapie cellulaire adoptive



(Carter et al., 1992)
(Larkin et al., NEJM 2015)
(Yu et al., Exp Ther Med 2016)

Déverrouiller
Le système immunitaire

Immunothérapie passive

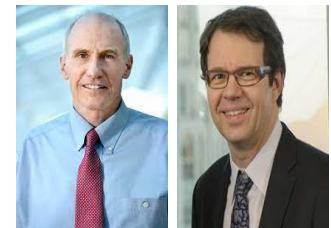
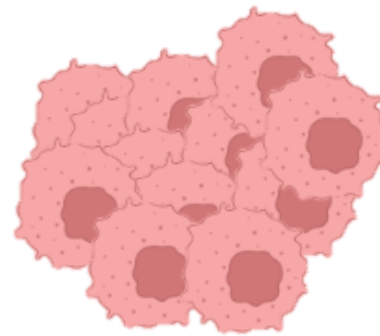


Inhibiteurs
checkpoints
immunologiques
(Nivolumab : PD-1
Ipilimumab : CTLA-4)

Anticorps
Monoclonaux
(Rituximab : CD20
Trastuzumab : HER2)



Anti-angiogénèse
(Bevacizumab : VEGF)



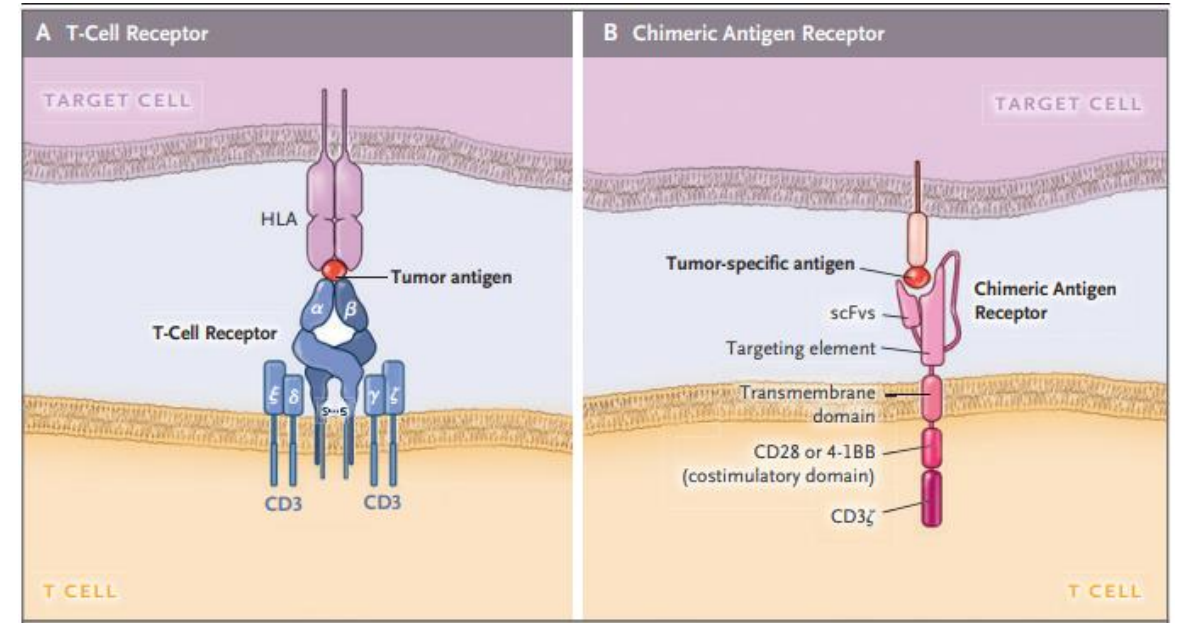
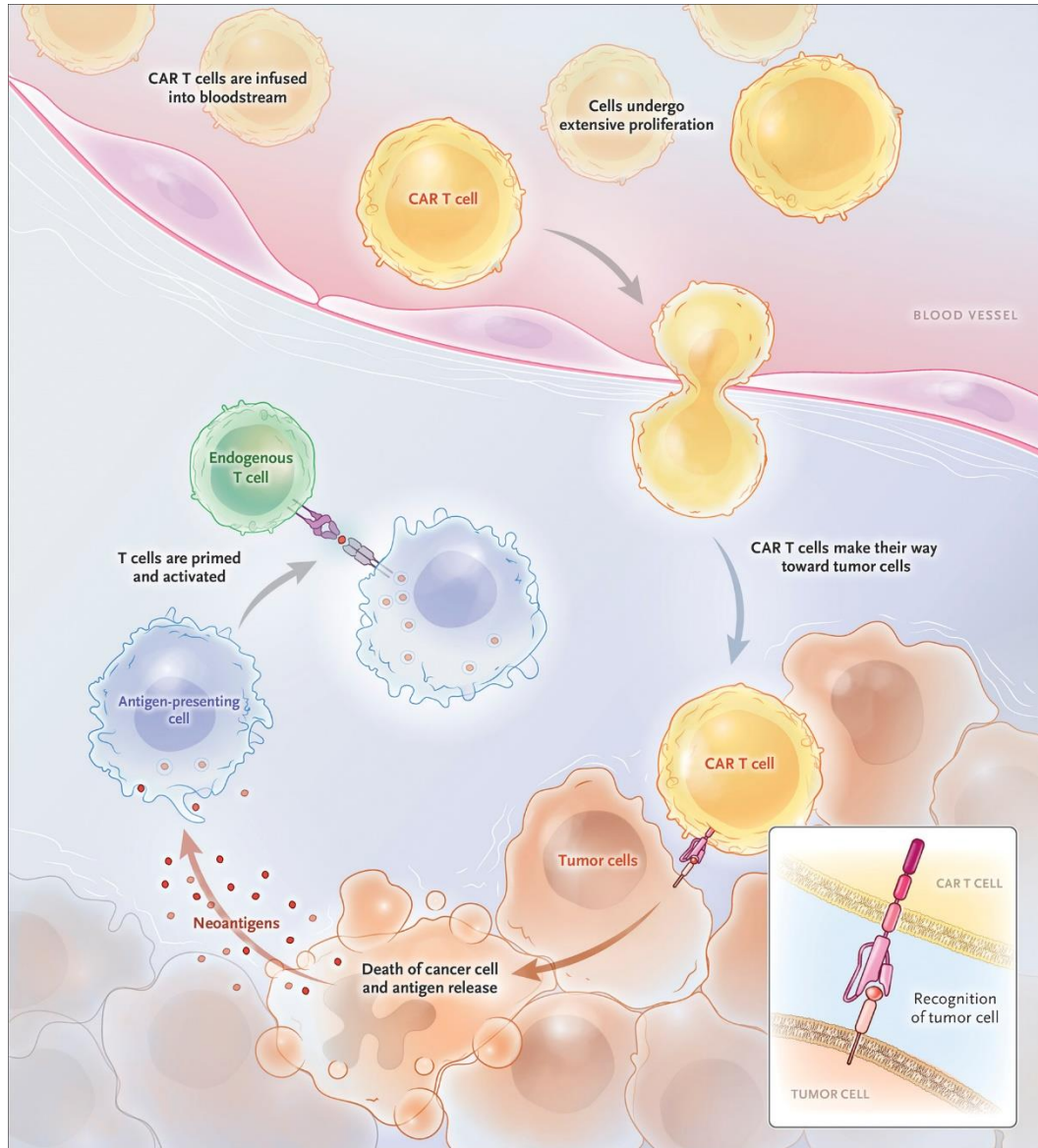
Pr Carl H. JUNE et Pr Michel SADELAIN

Prix Nobel de Médecine 2018

Pr James ALLISON et Pr Tasuku HONJO

CAR T-cell : une thérapie cellulaire adoptive

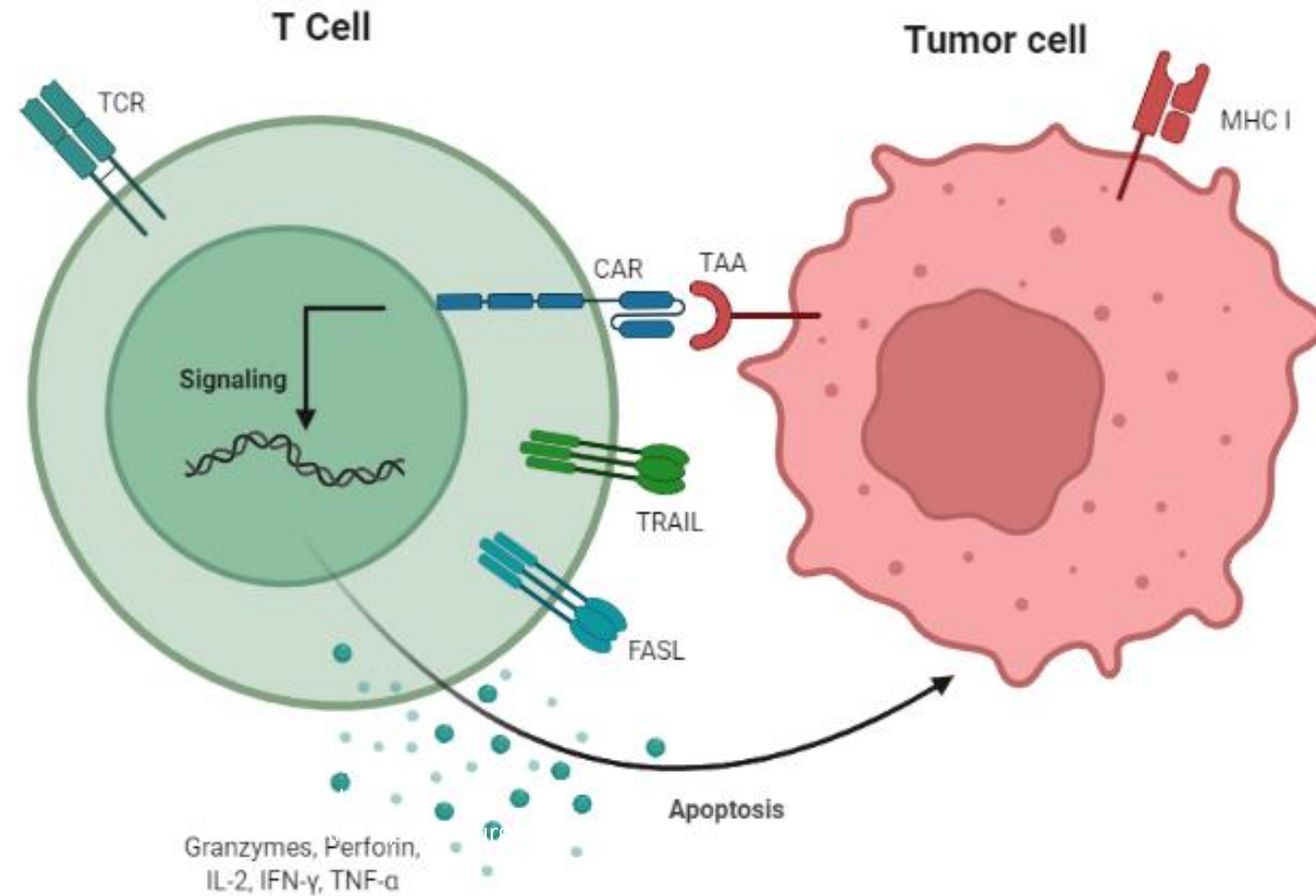
Chimeric Antigen Receptor T-cell



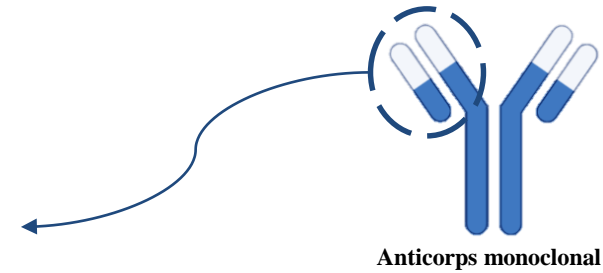
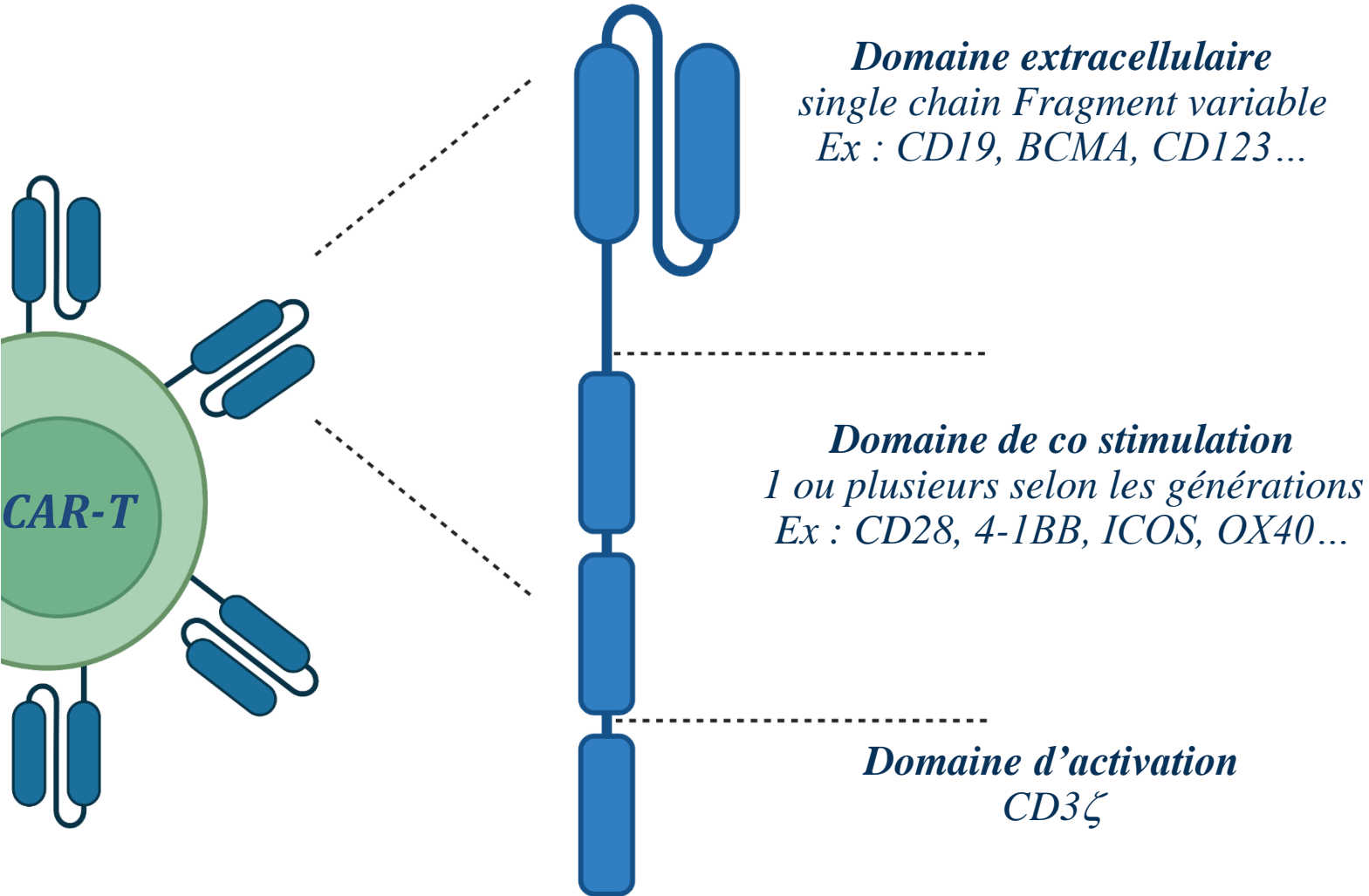
CAR comprend :
Un domaine cytoplasmique
+
Un domaine de reconnaissance extra cellulaire

Immunothérapie antitumorales à base de cellules génétiquement modifiées : les CAR-T cells

Chimeric Antigen Receptor T lymphocyte : lymphocyte T génétiquement modifié



De quoi est composé un CAR ?



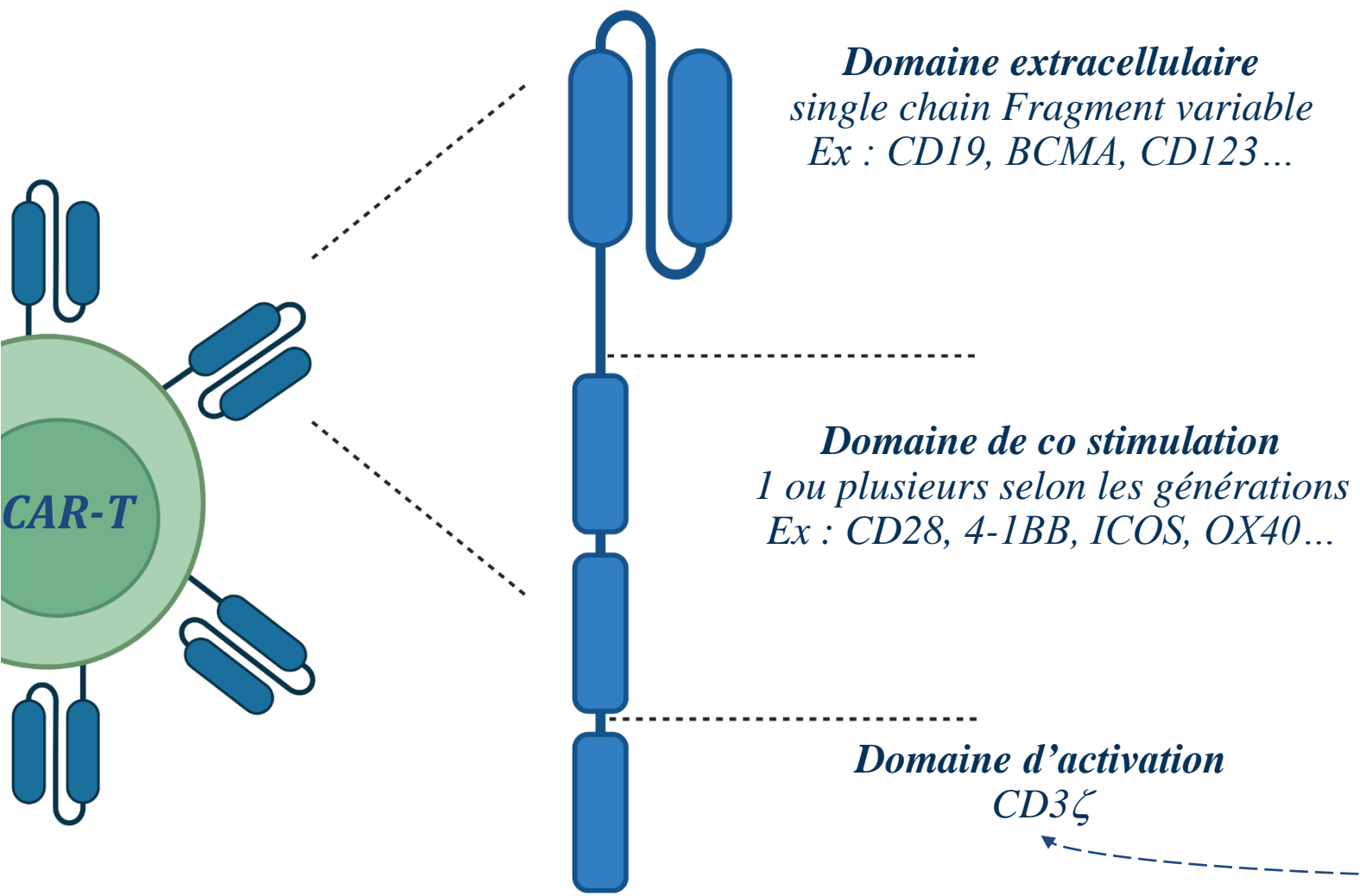
Elément de reconnaissance d'un Ag à la surface des cellules tumorales

Reconnaissance de la « cible »

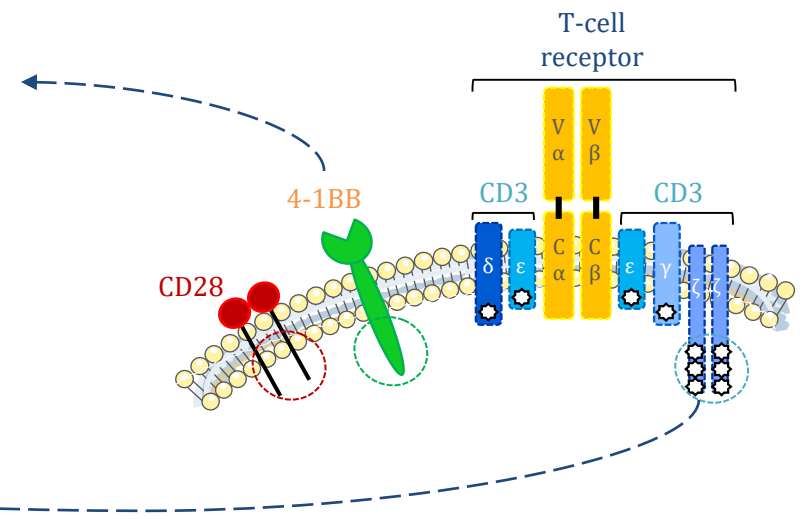
**Le plus spécifique possible
Eviter destruction cellules
physiologiques**

on-target/off-tumor effect

De quoi est composé un CAR ?



Eléments intracellulaires
Activation LT
Engager des mécanismes de **destruction** des cellules cibles

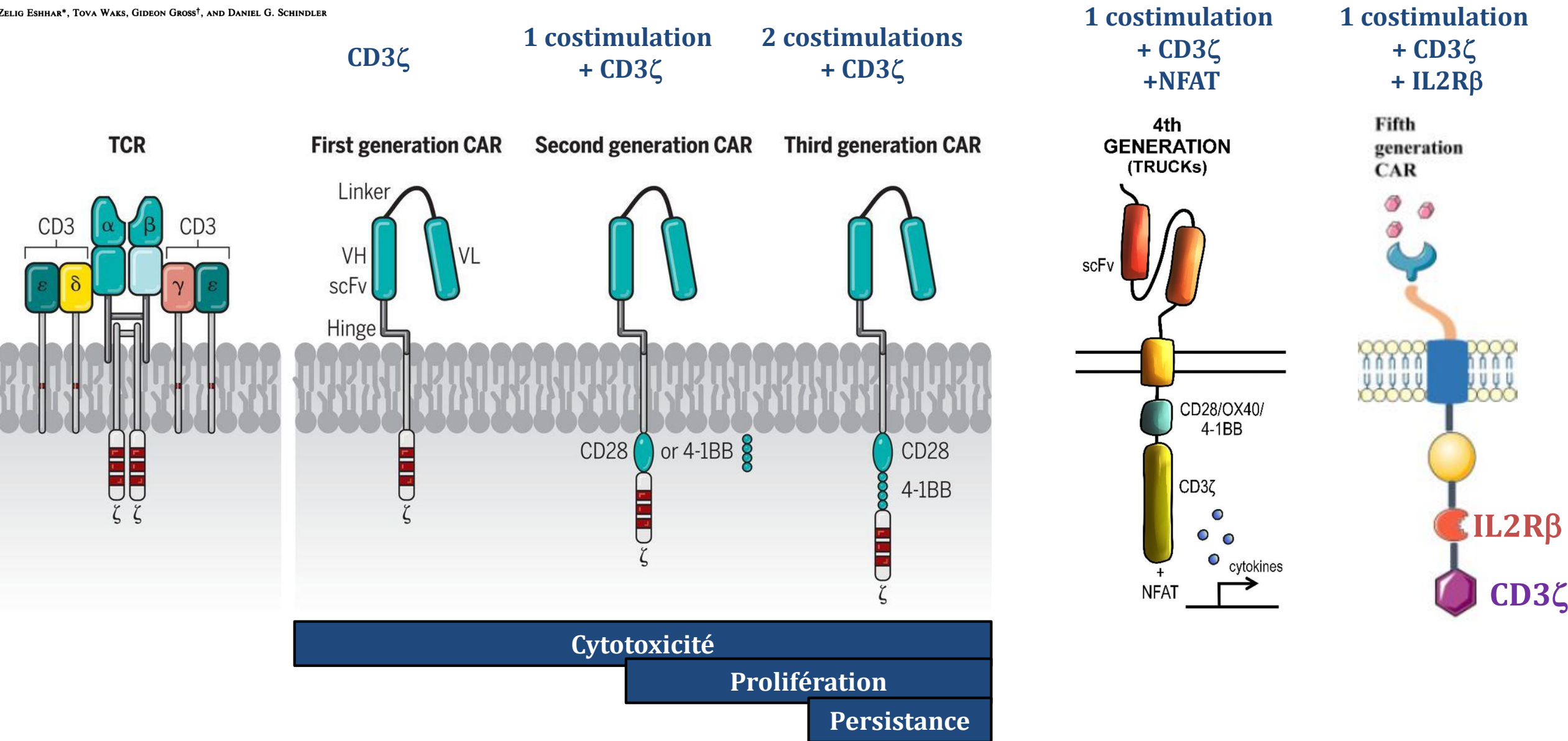


Les différentes générations de CAR-T

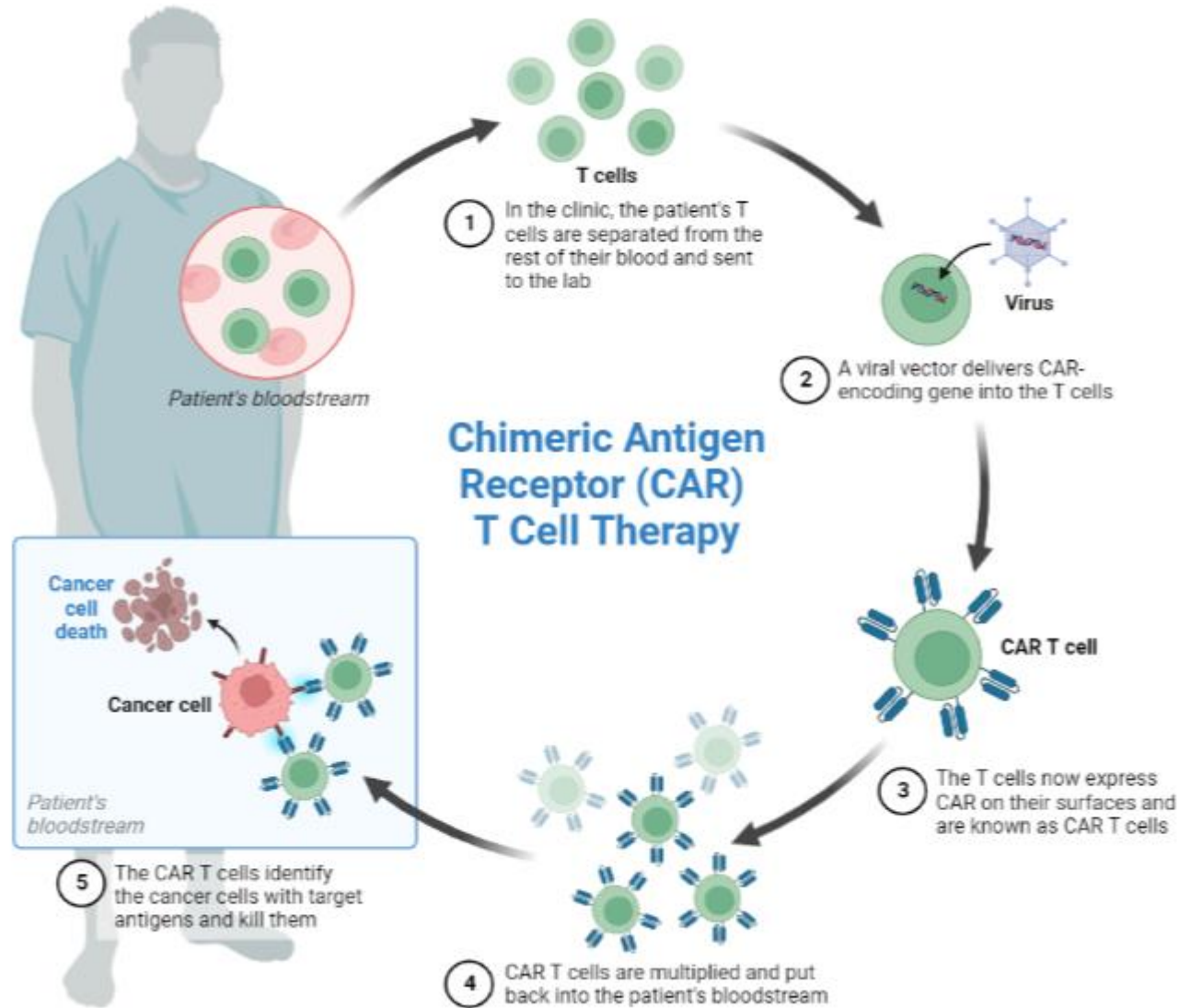
Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the γ or ζ subunits of the immunoglobulin and T-cell receptors

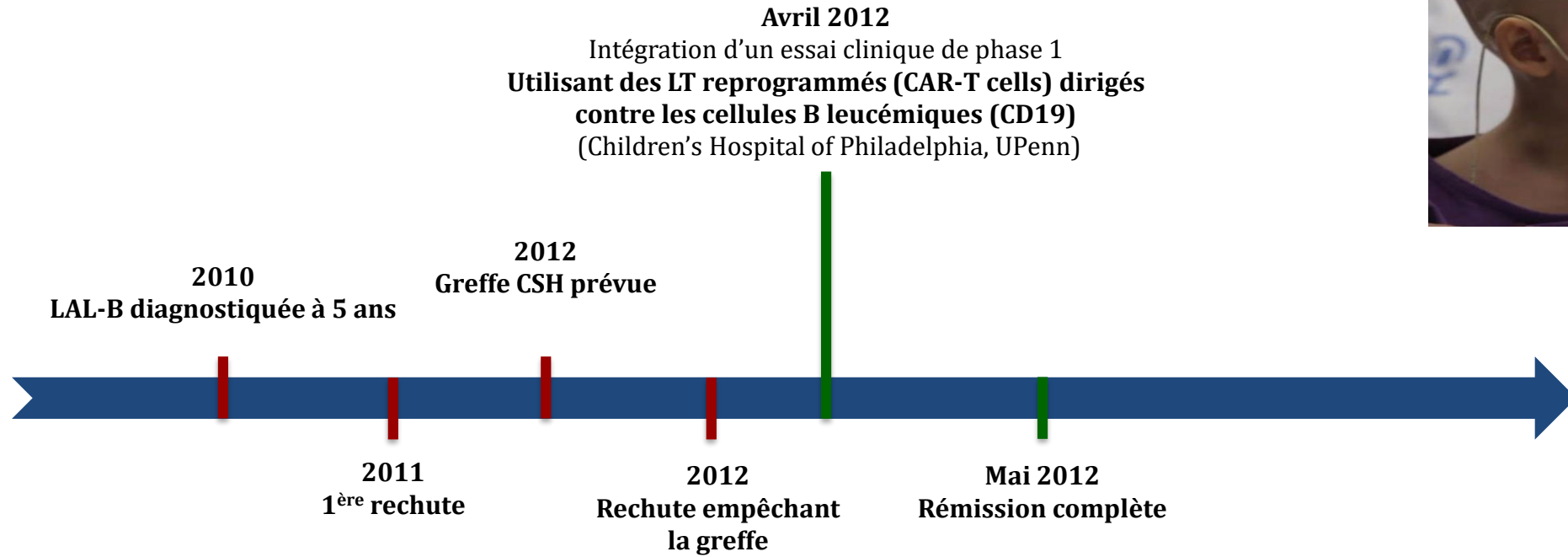
(single-chain Fv domain/chimeric receptors/immunotargeting/T cell)

ZELIG ESHHAR*, TOVA WAKS, GIDEON GROSS†, AND DANIEL G. SCHINDLER



Fabrication des CAR-T







2023
Absence de cancer



Les CAR académiques en recherche : exemple du CAR123

Immunotherapy

Leukemia, 2020

CD28/4-1BB CD123 CAR T cells in blastic plasmacytoid dendritic cell neoplasm

Elodie Bôle-Richard¹ · Maxime Fredon¹ · Sabeha Biichlé¹ · François Anna^{2,3} · Jean-Marie Certoux¹ · Florian Renosi¹ · Frédéric Tsé¹ · Chloé Molimard⁴ · Séverine Valmary-Degano⁴ · Alizée Jenvrin¹ · Walid Warda¹ · Jean-René Pallandre¹ · Francis Bonnefoy¹ · Margaux Poussard¹ · Marina Deschamps¹ · Tony Petrella⁵ · Christophe Roumier⁶ · Elizabeth Macintyre⁷ · Frédéric Féger⁸ · Eolia Brissot⁸ · Mohamad Mohty⁸ · Kiave-Yune HoWangYin⁹ · Pierre Langlade-Demoyen² · Maria Loustau² · Julien Caumartin² · Yann Godet¹ · Delphine Binda^{1,10} · Maïder Pagadoy¹⁰ · Eric Deconinck^{1,11} · Etienne Daguindau^{1,11} · Philippe Saas¹ · Christophe Ferrand¹ · Fanny Angelot-Delettre¹ · Olivier Adotévi^{1,12} · Francine Garnache-Ottou¹

Check for updates

Article

Umbilical Cord Blood as a Source of Less Differentiated T Cells to Produce CD123 CAR-T Cells

Cancers, 2022

Blandine Caël¹, Jeanne Galaine¹, Isabelle Bardey², Chrystel Marton^{1,3}, Maxime Fredon¹, Sabeha Biichle¹, Margaux Poussard¹, Yann Godet¹, Fanny Angelot-Delettre^{1,4}, Christophe Barisien⁵, Christophe Bésiers⁴, Olivier Adotevi^{1,6}, Fabienne Pouthier², Francine Garnache-Ottou^{1,†} and Elodie Bôle-Richard^{1,*,†}



BPDCN: When polychemotherapy does not compromise allogeneic CD123 CAR-T cell cytotoxicity

eJHaem, 2020

Margaux Poussard^{1,*} | Laure Philippe^{2,*} | Maxime Fredon¹ | Elodie Bôle-Richard¹ | Sabeha Biichle¹ | Florian Renosi¹ | Sophie Perrin³ | Marie Kroemer³ | Samuel Limat³ | Francis Bonnefoy¹ | Etienne Daguindau^{1,4} | Eric Deconinck^{1,4} | Bérengère Gruson⁵ | Philippe Saas¹ | Olivier Adotévi^{1,6} | Francine Garnache-Ottou^{1,7} | Fanny Angelot-Delettre^{1,8}

Evaluation of the impact of scFv on functionality and safety of 3rd generation CD123 CAR T-cell

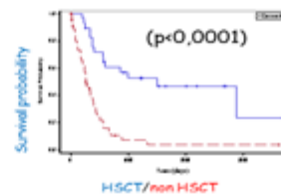
Frontiers in Immunol, submitted, 2023

Maxime Fredon¹, Margaux Poussard¹, Sabeha Biichle¹, Francis Bonnefoy¹, Charles-Frédéric Manton¹, Evan Seffar^{1,4}, Florian Renosi¹, Elodie Bôle-Richard¹, Romain Boidot⁵, François Anna^{2,3}, Maria Loustau², Julien Caumartin², Mathieu Gonçalves-Venturelli^{1,6}, Eric Robinet⁶, Philippe Saas¹, Eric Deconinck^{1,7}, Etienne Daguindau^{1,7}, Xavier Roussel¹, Olivier Adotévi^{1,4}, Fanny Angelot-Delettre¹, Jeanne Galaine^{1,†}, Francine Garnache-Ottou^{1,8†}



French national network **ROMI**

TumeuRes à Cellules Dendritiques PlasmOctoïdes et HéMopathIeS avec pDC
#DC2016-2791

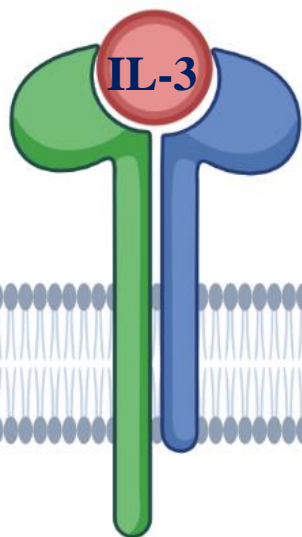


N=86
Garnache-Ottou, E
Deconinck et al., Blood Adv., 2020



- Pr F Garnache Ottou
- Pr Olivier Adotevi
- Dr Fanny Delette
- Dr Yan Godet
- Dr Jeanne Galaine
- Dr Florian Renosi
- Dr Elodie Bole Richard
- Maxime Fredon
- Sabaha Biichle
- Patricia Letondal
- Blandine Caël
- Charles Frederic Mantion
- Xavier Roussel
- Valentin Pourchet

β -subunit
(CD131)



α -subunit
(CD123)



BPDCN

AML

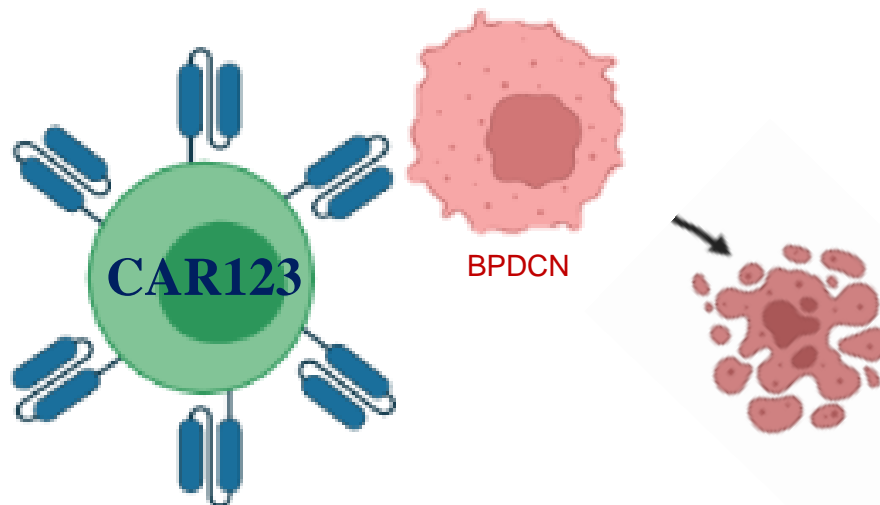
ALL

2021
Laboratoire de Biologie médicale de référence

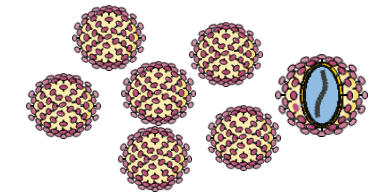
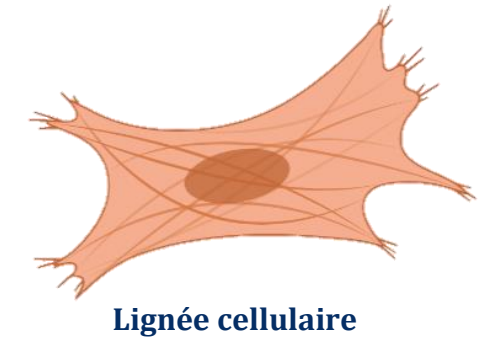
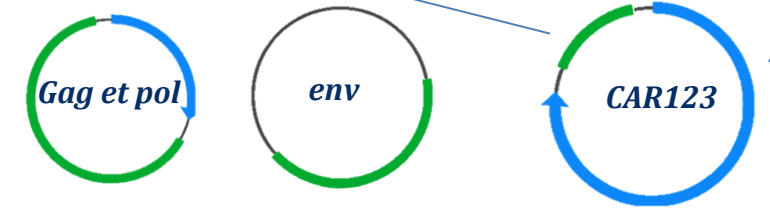
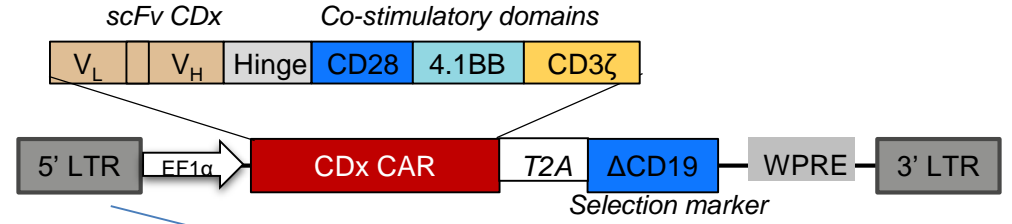
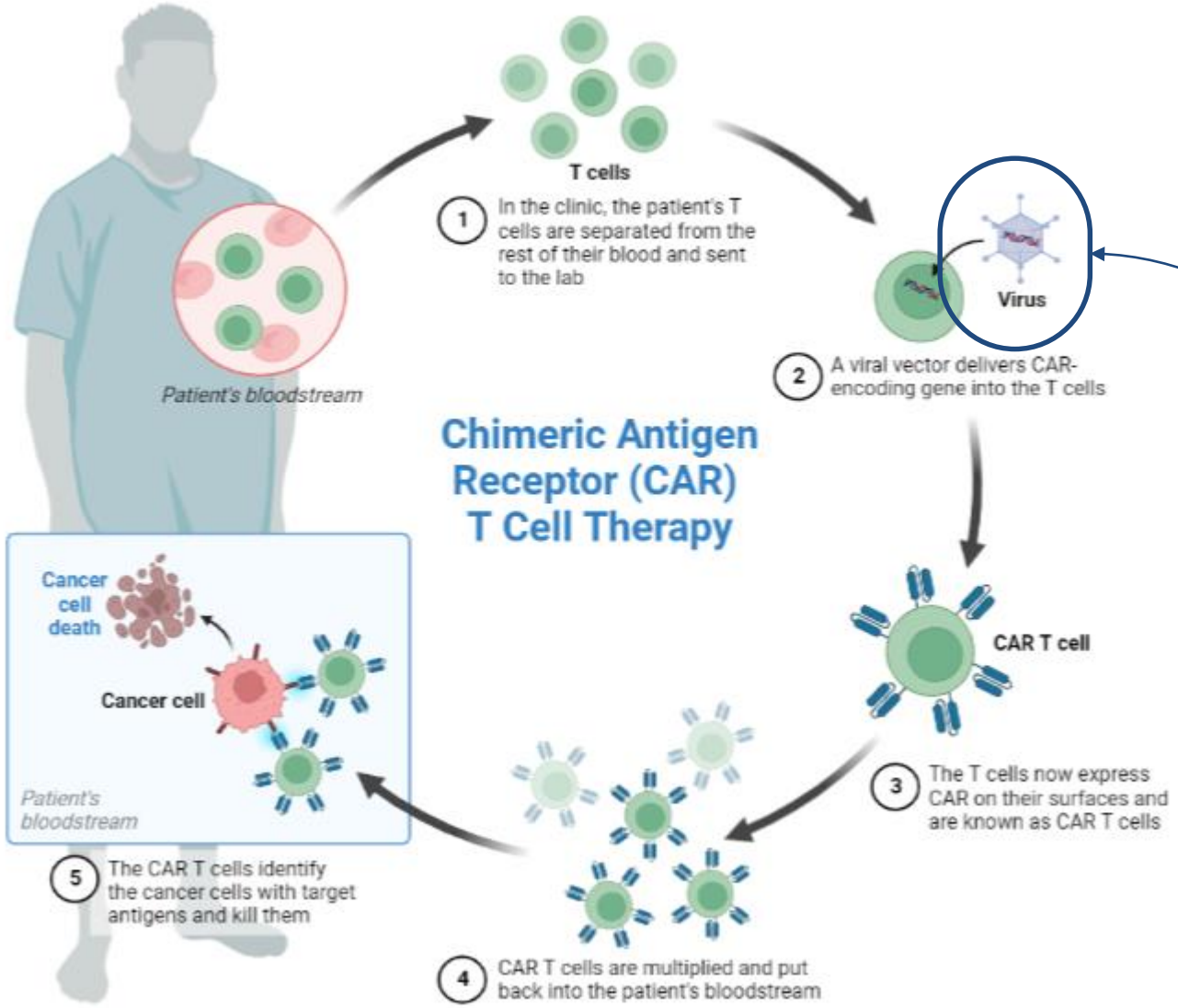


(Déclaration ministériel JORF n°0167 21 juillet 2021)

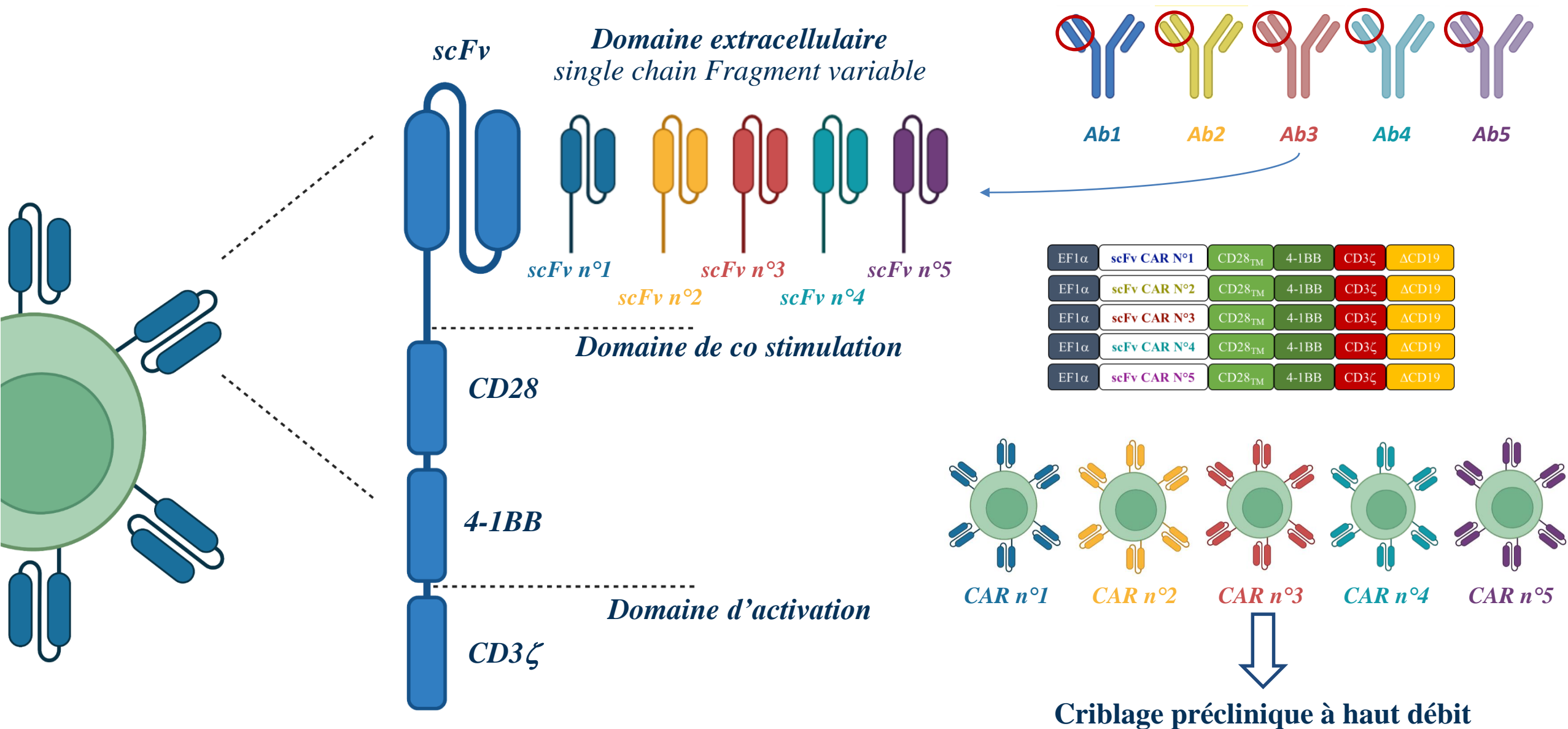
2015
CAR T
pour traiter Leucémies pDC
CAR123



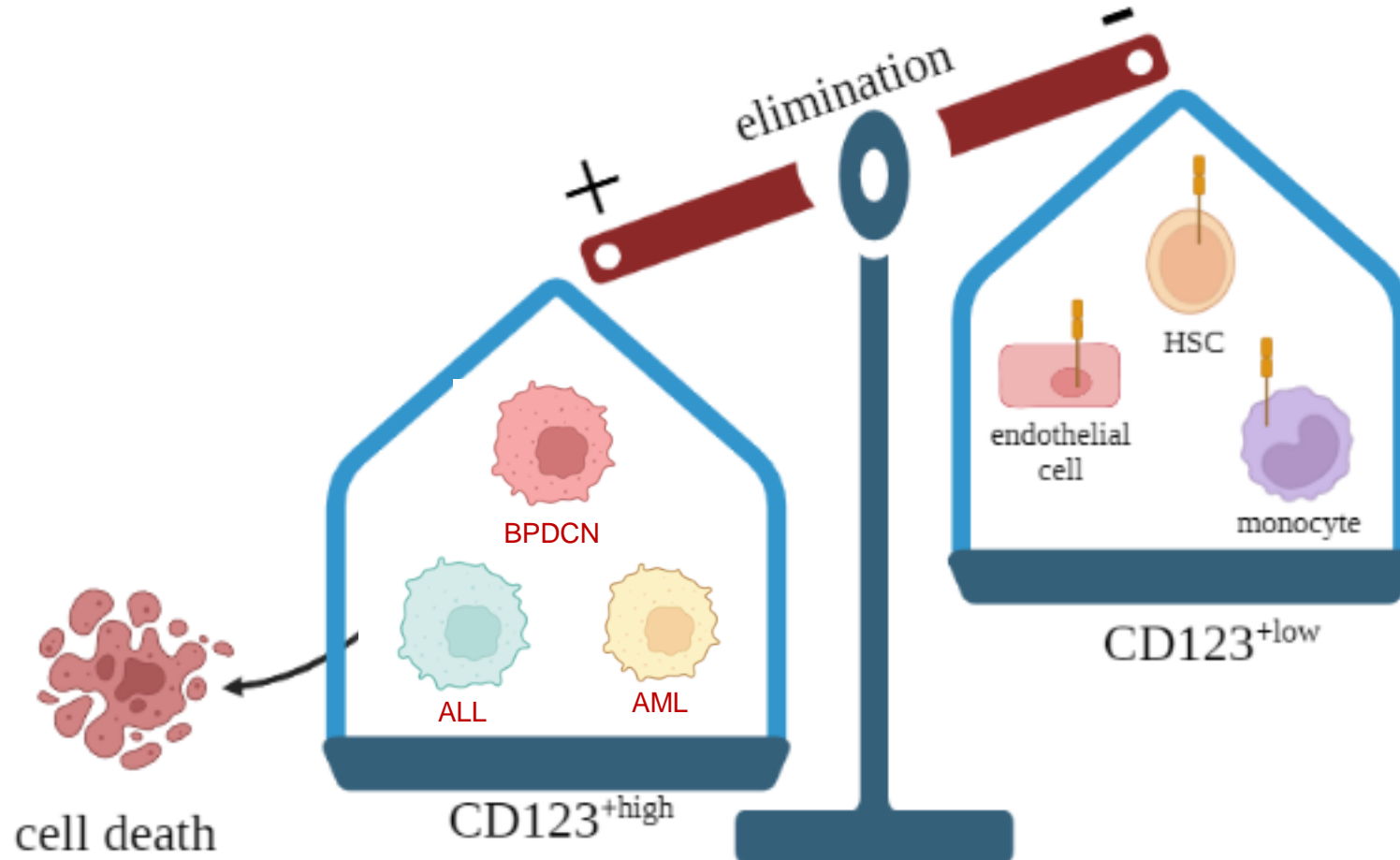
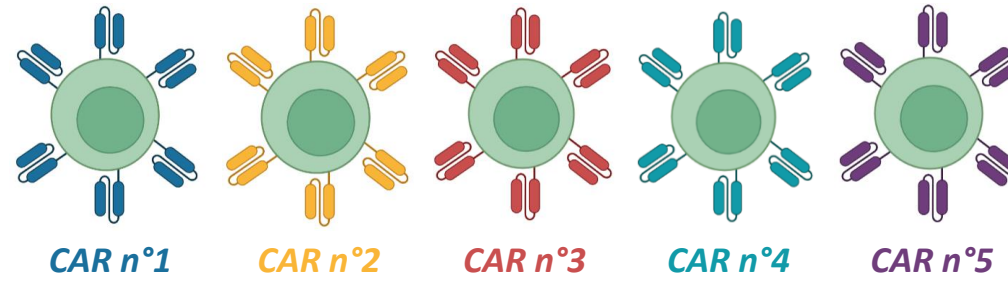
Comment produire des CAR-T en recherche

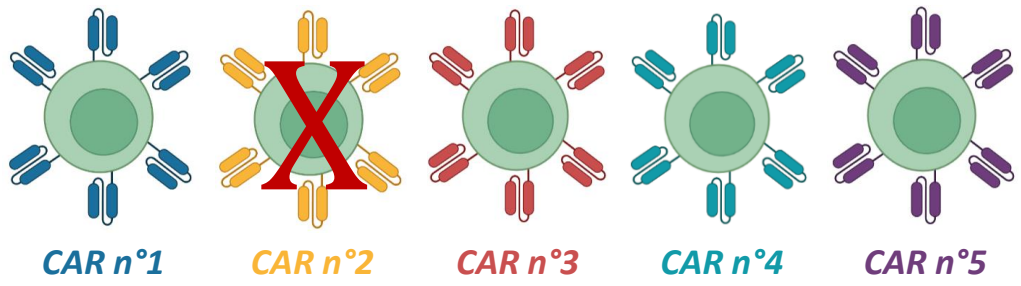


Développement recherche de CAR123

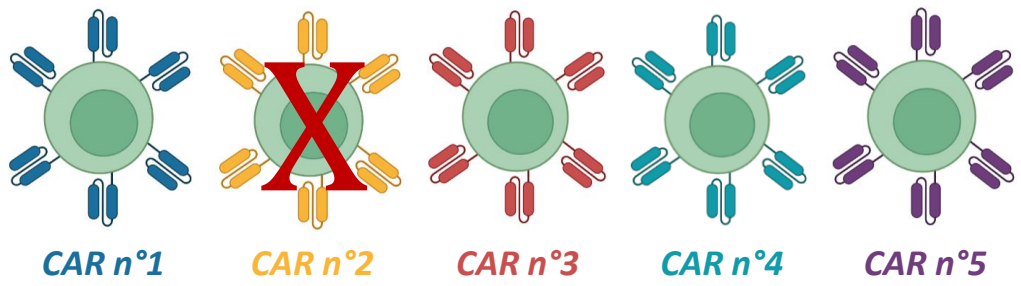


Développement recherche de CAR123

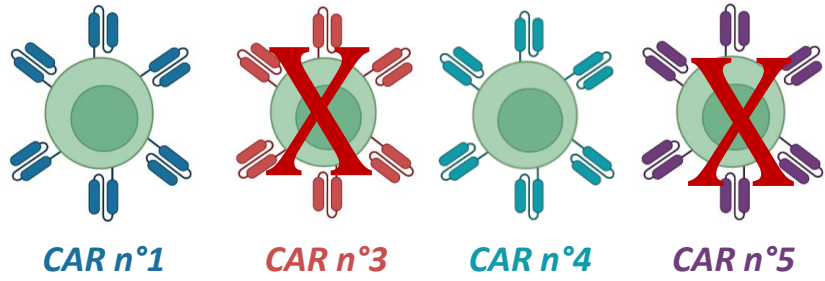




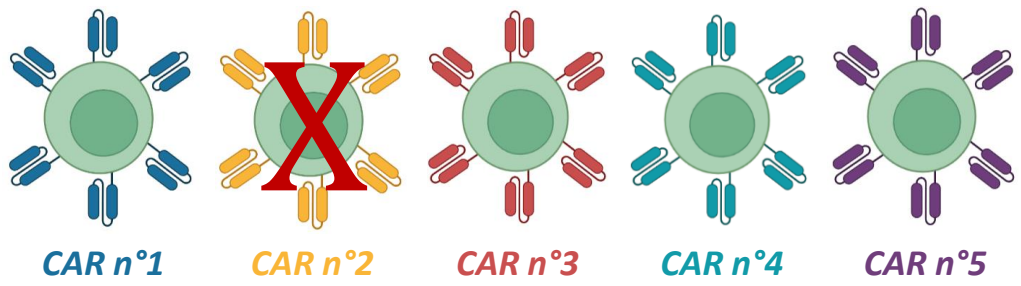
CD123 CAR-T production
(Transduction efficiency/ CAR expression)



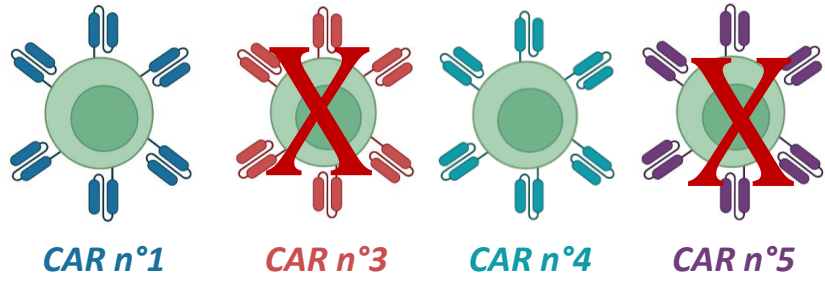
CD123 CAR-T production
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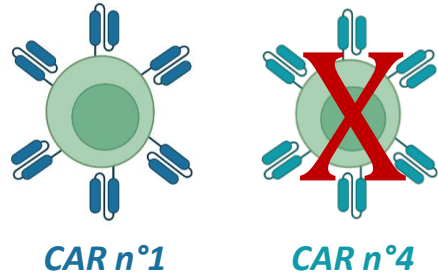
in vitro functionality vs BPDCN and monocyte and endothelial cell
(CD107a/7-AAD/cytokine secretion)



CD123 CAR-T production
(Transduction efficiency/ CAR expression)

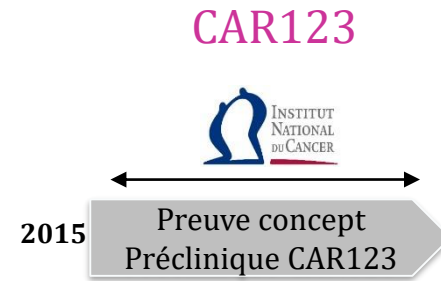


in vitro functionality vs BPDCN and monocyte and endothelial cell
(CD107a/7-AAD/cytokine secretion)



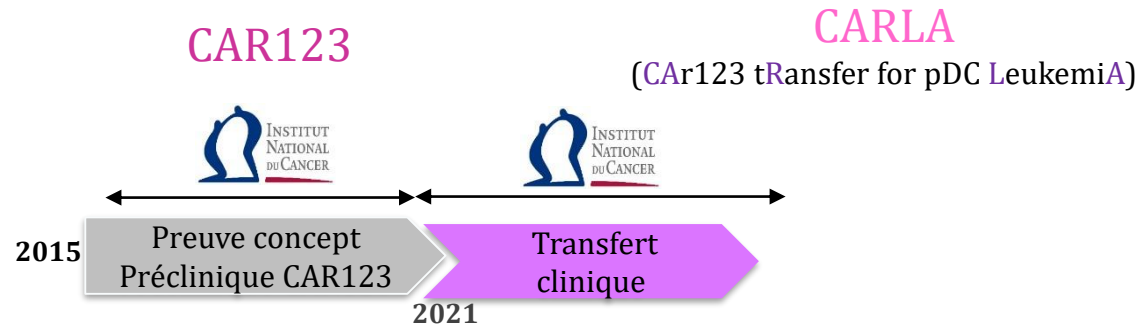
in vivo functionality (CAL-1/PDX/Gen2.2)

Développement clinique du CAR123

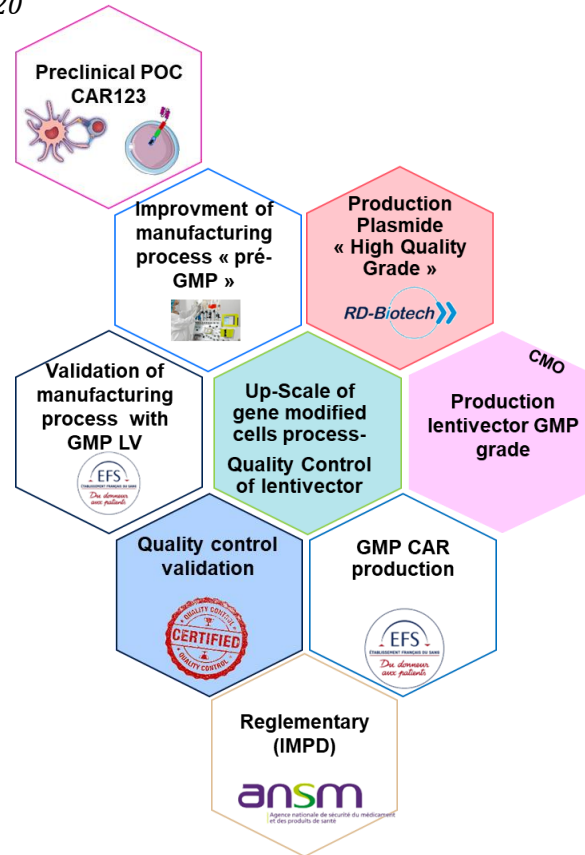


✓ *Bôle-Richard et al,
Leukemia 2020*

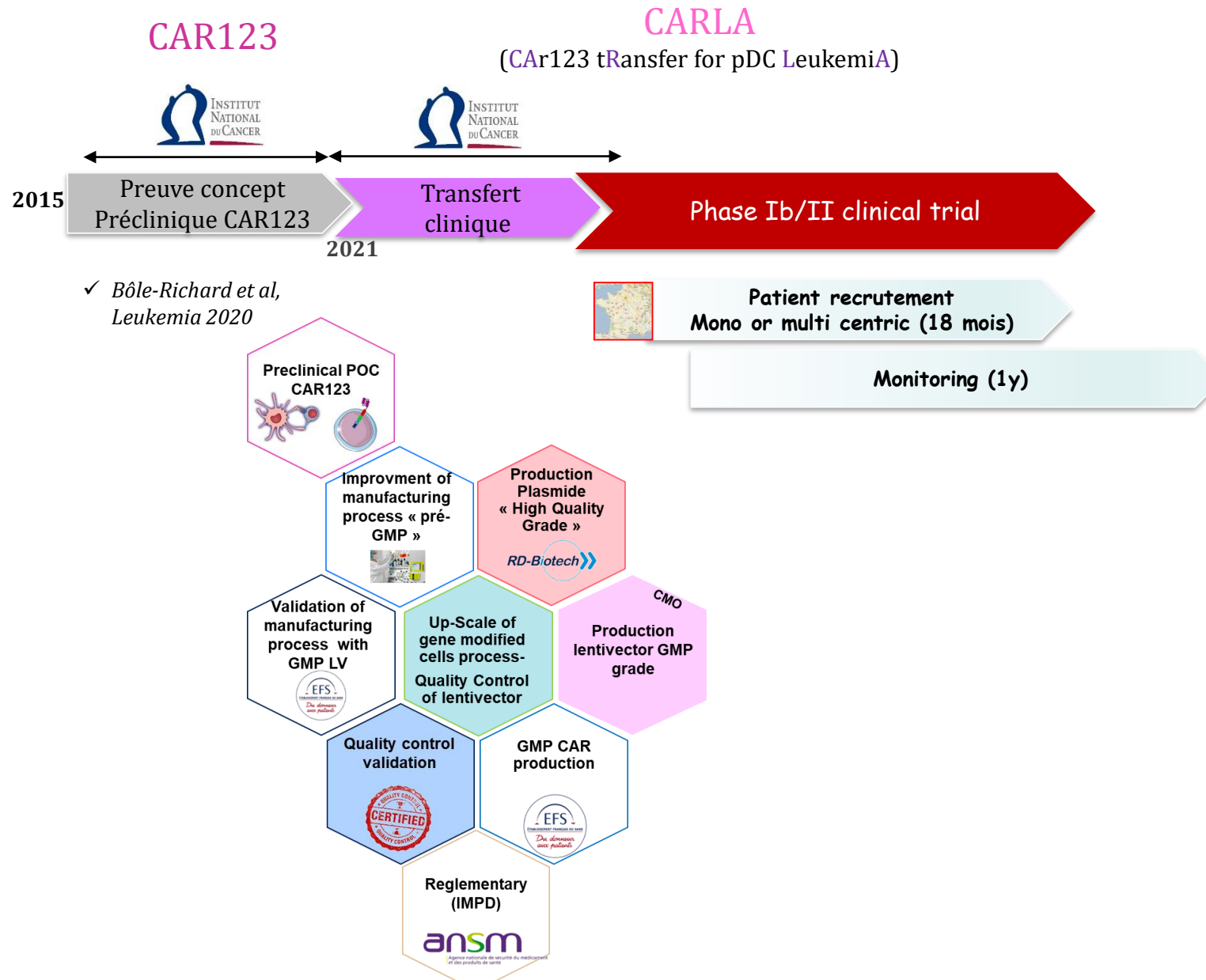
Développement clinique du CAR123



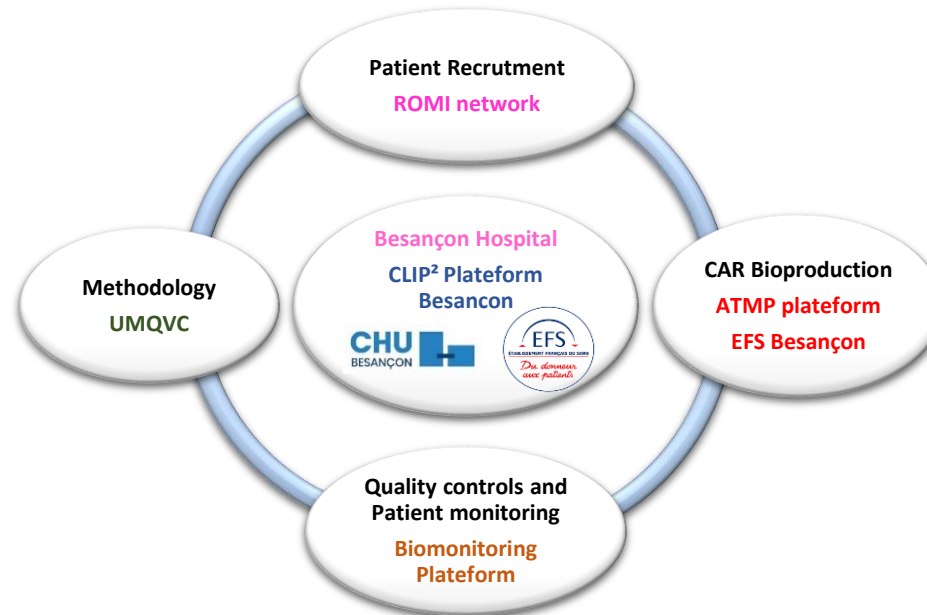
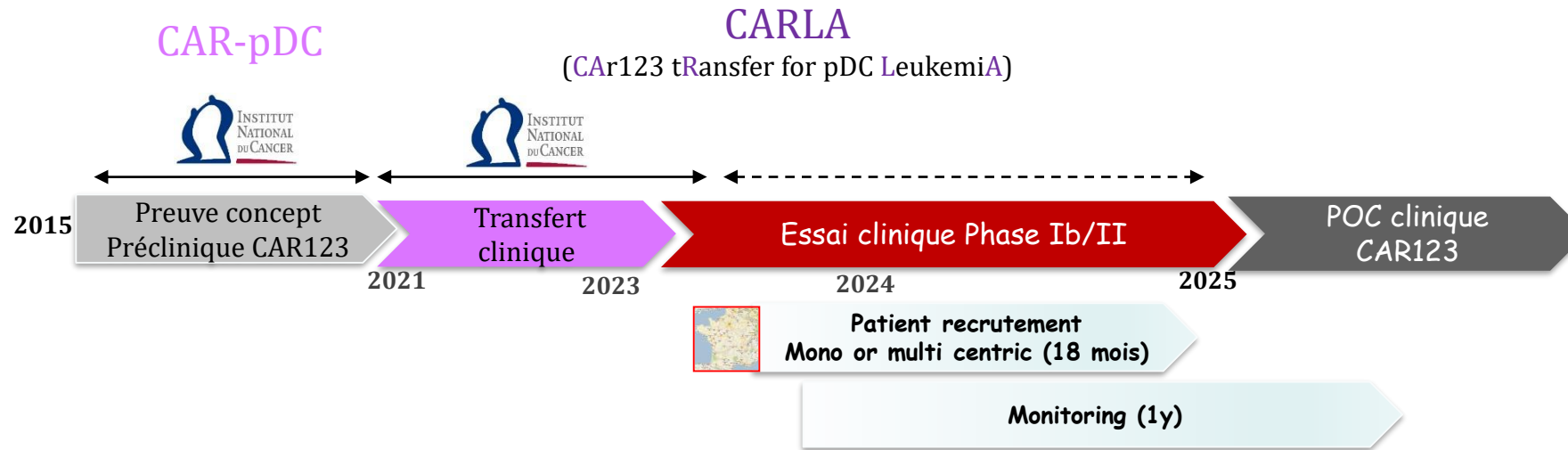
✓ Bôle-Richard et al,
Leukemia 2020



Développement clinique du CAR123



Développement clinique du CAR123



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O ADOTEVI

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Y GODET
F DELETTRE
E BOLE-RICHARD
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J GALAINE
C BORG
S BIICHLE
M FREDON
R LOYON
M POUSSARD
CA MANTION
M BOICHUT
X ROUSSEL
P LETONDAL
I BELAKRI

**EFS-Immunologie-
Cytologie- Biologie
Moléculaire**
T FOURNET, A ROGGY, S
PUYRAIMOND, V
MATHIEU, F LEJARRE,
F RENOSI, C FERRAND
Et toutes les équipes

AICT- MTI
F POUTHIER, S ROUX, J
GALAINE
Toute l'équipe

CHU Besançon

Pr Eric DECONINCK
Dr Etienne DAGUINDAU
Dr Ana Berceau
Dr Yohan Desbrosses
Dr Marion Simonet
Dr Adrien Chauchet
Dr Xavier Roussel

PIBT

C GAMONET
J DESNOUVEAUX
E BÔLE RICHARD

**Plateforme
Biomonitoring**
C LAHEURTE
Toute l'équipe

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A GALY, C FOURNIER, A
BIEK

F. Acard, I. Arnoux, V. Asnafi, L. Baseggio, MC. Bene, Bouyer S, O Calendini, L. Campos, M. Capbern, JP. Capiod, L. Chaperot, B. Chatelain, S. Daliphard, M Diaby, M. Degenne, F. Delhommeau, B. Drenou, E. Duchayne, E Guerin, F Trimoreau, C. Dupret, A. Falkenrodt, P. Felman, T. Fest, J. Feuillard, V. Foissaud, C. Fourcade, R. Garand, C. Garandeau, MC. Jacob, E. Jobert, E. Kuhlein, M Legarff Tavernier, F. Lellouche, P. Lepelley, D. Leroux, V. Leymarie, D. Lusina, E. Macintyre, V. Mathieu, M. Maynadié, P. Mosckoventchko, ME. Noguera, T. Petrella, F. Picard, J. Plumas, S. tarfi, C. Preudhomme, C. Roumier, M. Rousset, V. Salaun, F. Schillinger, F. Solly, P. Saussoy, C. Trichet, X. Troussard, C. Vasselon, B. Chatelain, L. Baseggio, C. Arnoulet, A. Debliquis, J. Guy, H. Benanni, A. Plesia, L. Vila, F. Geneviève, G. Le Calvez, Z. Benseddik, R. Veyrat, D. Mallet, C. Roumier, R. Lacroix, B. Benet, P. Okamba, C. Bret, N Legay, V. Latget Canard, V. Asnafi, C. Brouzes, L. Lhermitte, V Saada, C Basle, C Buors, G Buchonnet, H Broutier, E Bera, C Boutet, E Bonin, J Osman, J Rose, M. Ticchioni, S. Brun, B Badaoui, A. Arnaud, V Harrivel, T Boyer, D. Lusina, R. Letestu, V. Bardet, J Zhu, A Maillon, A Plat, O. Wagner Ballon, M. Legraff Tavernier, I Lemaire, C Salanoubat, F Genevieve, S Glasner, V Gelsi Boyer, E Guerrin, V Ragueneau, E Dincan, E. Dindineau, S. Bouyer, C Himberlin, E Cornet, AC Lhoumeau, R Shamieh, C Almire, R Veyrat Masson, I Arnoud, R Lacroix, M. Roussel, E Ronez, A. Galois, C. Mayer Rouse, M Tichionni, E Lainey, S Boyer, N Lechevalier, C Lafon

