Due to the character exclusively educational and eminently illustrative of the explanations in this presentation, the author accepts article 32 of the "*Ley de la propiedad intelectual*" (Law on Intellectual Property) in force regarding the partial use of works with images, graphics or other material contained in the different slides

All the images presented are included as necessary citations to illustrate the explanations of this class

ACCESO A TRATAMIENTOS ONCOLÓGICOS PARA PERSONAS CON CÁNCER
LA LUCHA ENTRE LA SUPERACIÓN Y LAS LIMITACIONES DEL SISTEMA

Acceso Tratamientos Oncológicos

FLS SCIENCE FOSTERING LEARNING & SHARING

BLOQUE I: Revisión de evidencias científicas de nuevos fármacos

Inmunoterapias celulares para pacientes con cáncer

Manel Juan i Otero, MD, PhD

Servei d'Immunologia – Centro de Diagnòstic Biomèdic. mjuan@clinic.cat

Hospital Clínic de Barcelona (HCB-FCRB) - IDIBAPS / Immunotherapy platform Hospital Sant Joan de Déu-HCB

Casa Covalescència, UAB, 17-02-2023; 10:00 h (40 min).

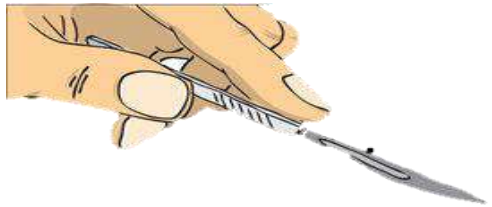
Clínic Barcelona | Universitat de Barcelona | IDIBAPS | Sant Joan de Déu

CONFLICT OF INTEREST - DISCLOSURES

- *No conflict by commercial interests or relationship with companies, except in what corresponds to **educational talks** sponsored by some companies and specific participations (2 meetings 2 years ago st least) as member of an Oncology Advisory Board of Grifols & Cytometry board of BD Biosciences, **no-related with CAR-T therapy**.*

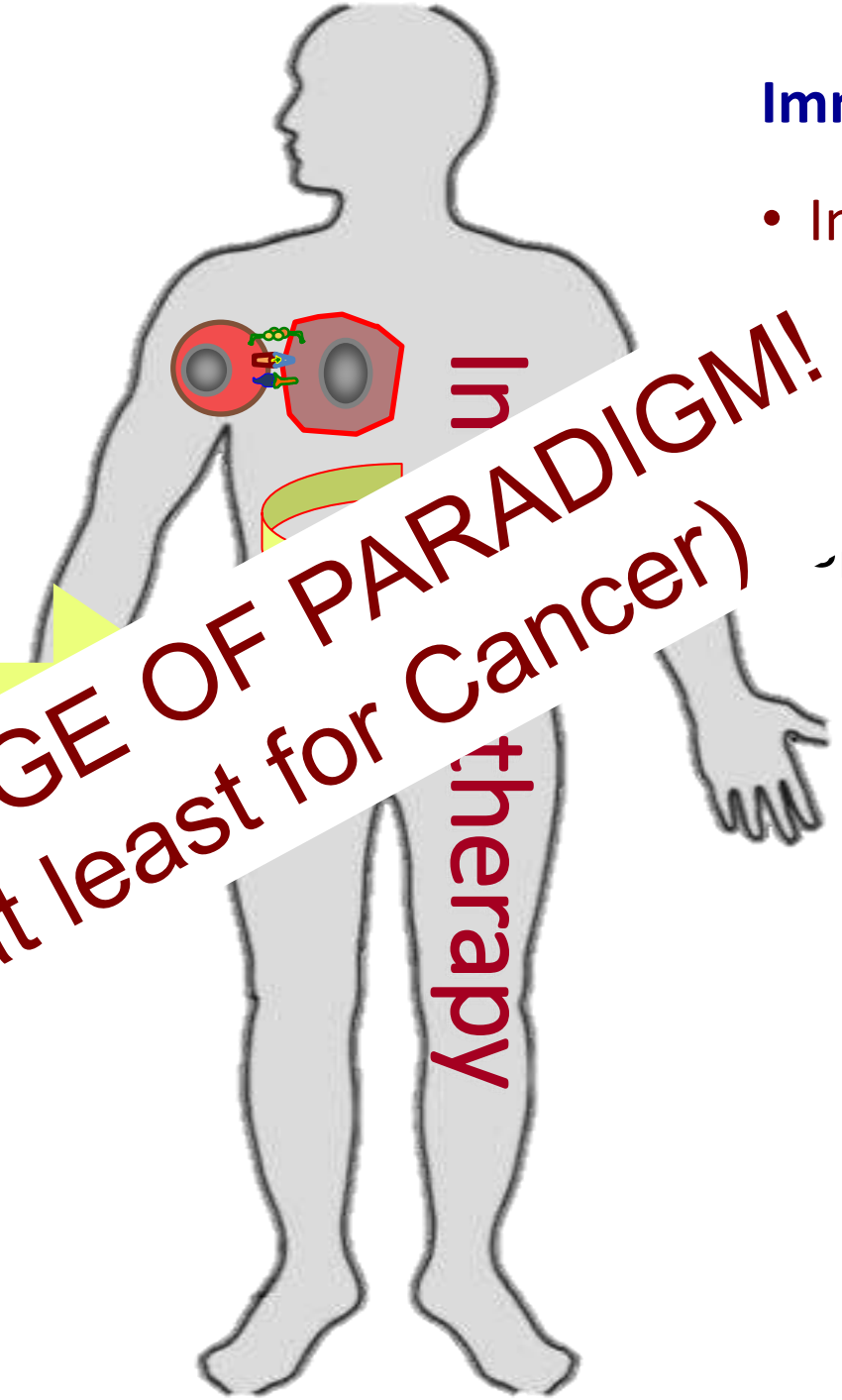
- Co-Responsible of production of academic CART product (ARI-0001, ARI002 & other ATMPs) in patients with B-cell malignancies (CART19-BE-01 & CARTBCMA-HCB-01 trials) (including some companies as Immuneel, Cocoon or Gyala) + Hospital Exemption by AEMPS … but **no-personal (economic) profit** from it.

Surgery



Conventional Drugs

Physical treatments:

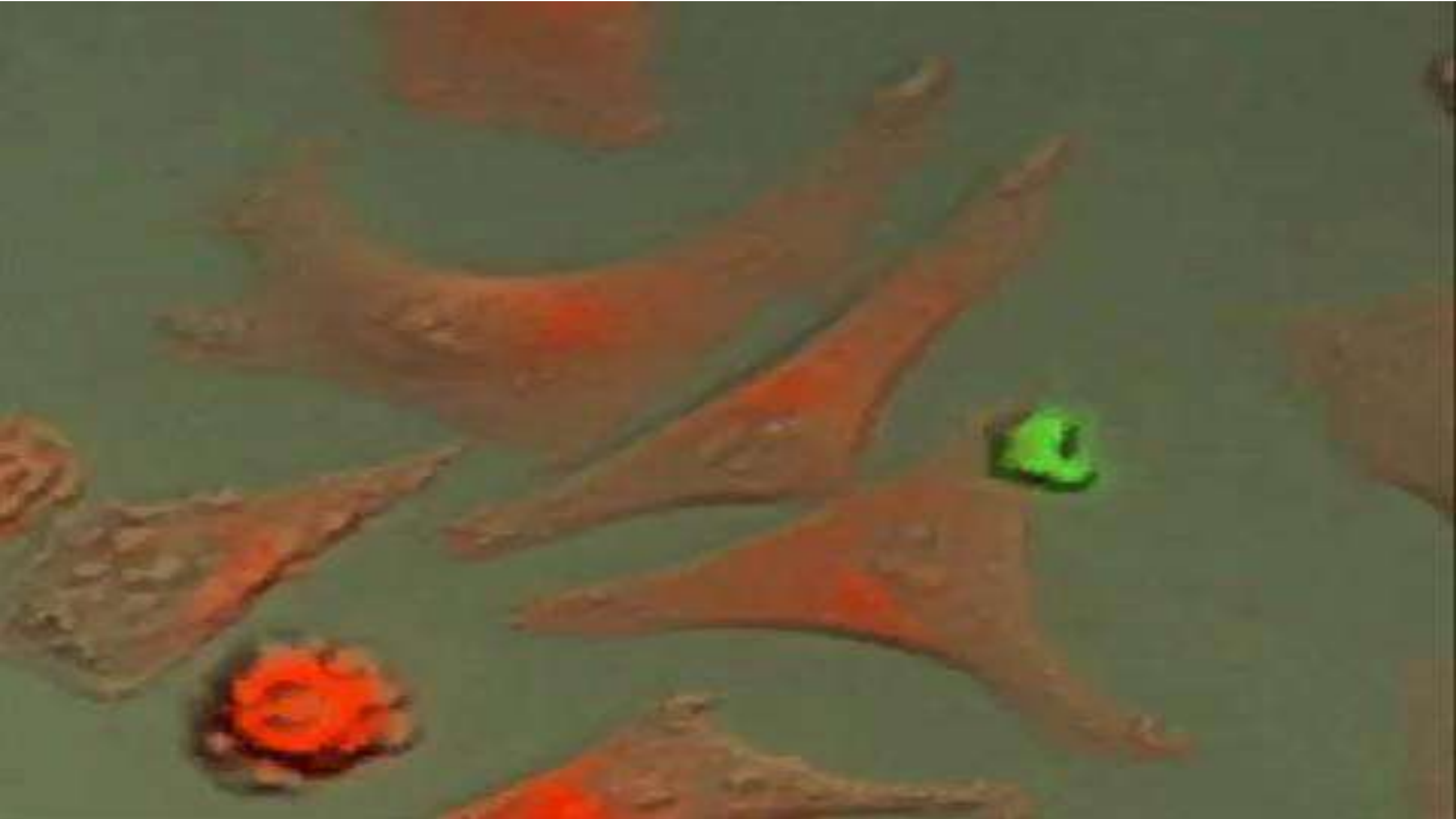


CHANGE OF PARADIGM!
(at least for Cancer)

In therapy

Immune System

- Internal (we already have it).
- inually effective (from infections).
- pecífic – target-directed



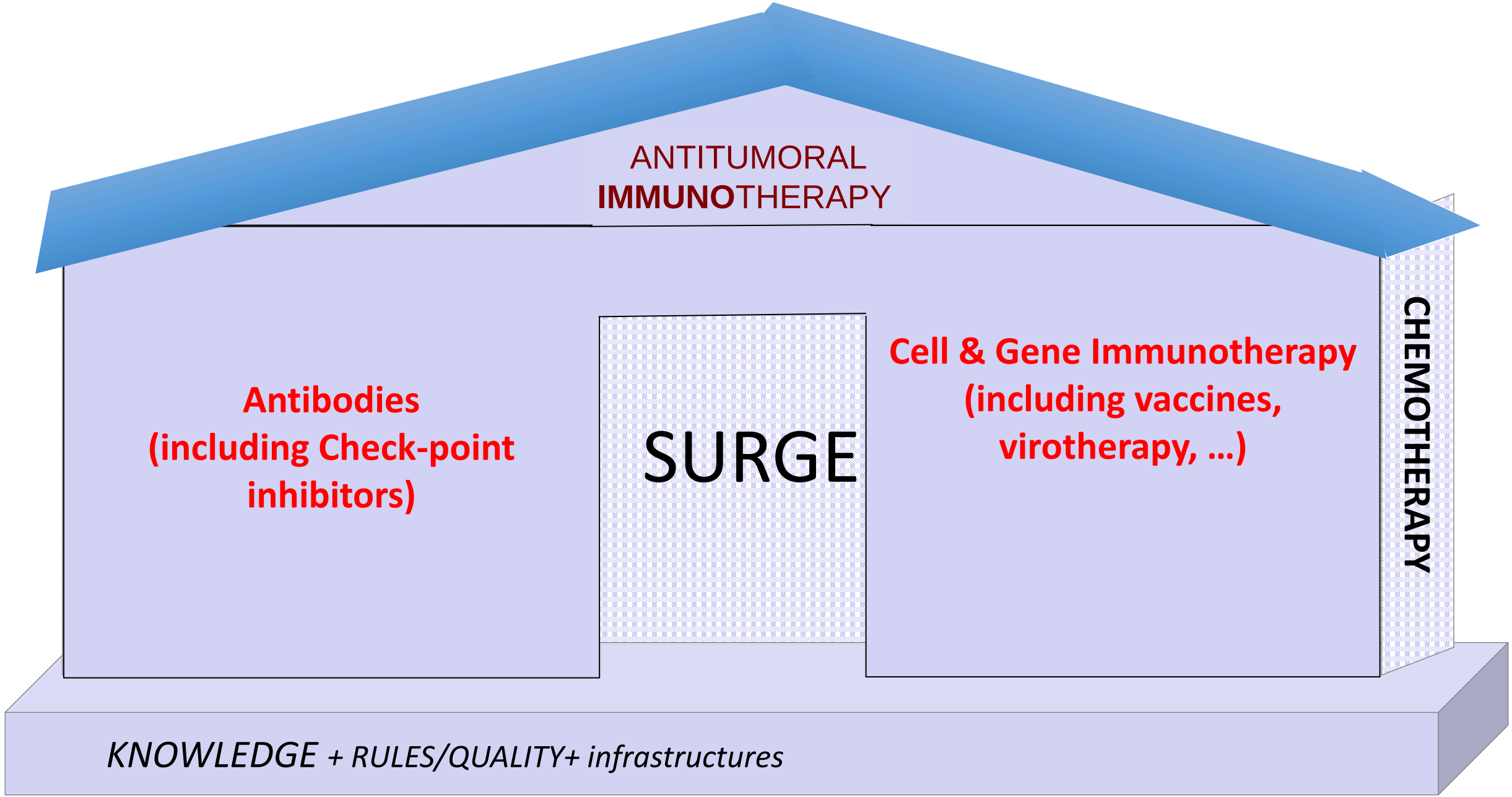


Figure by author

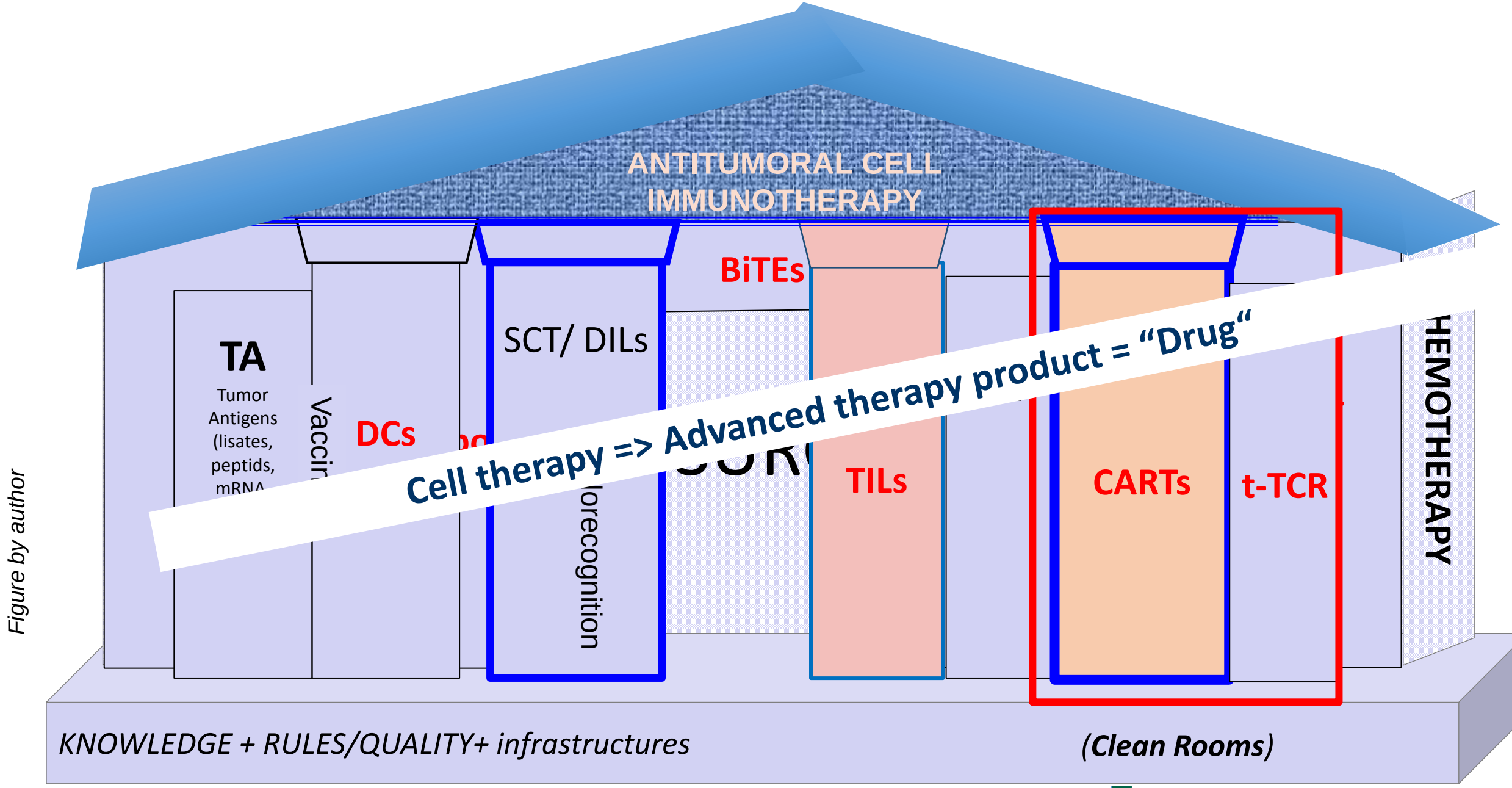
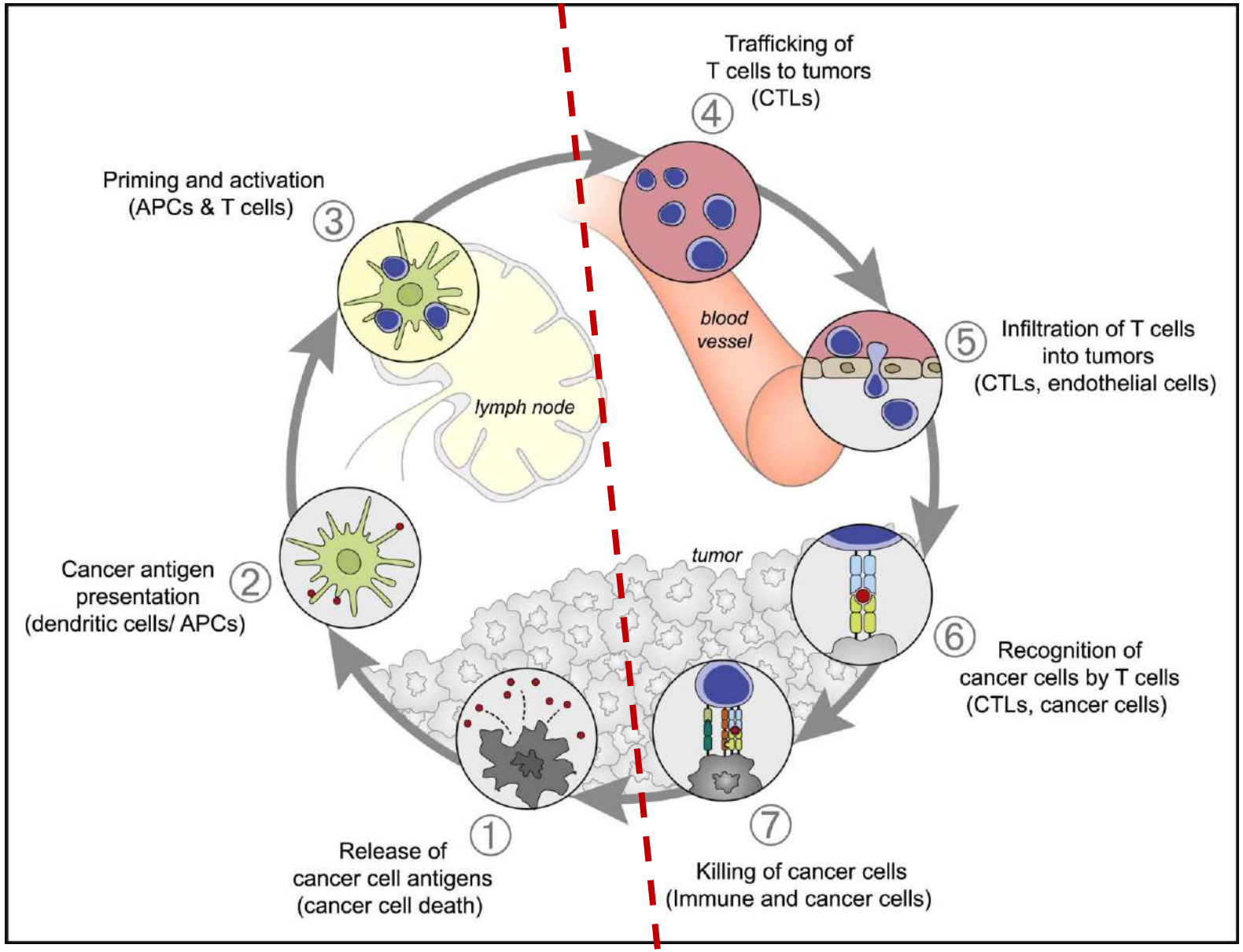


Figure by author



Chen DS, Mellman I. *Immunity.* 2013;39:1-10.

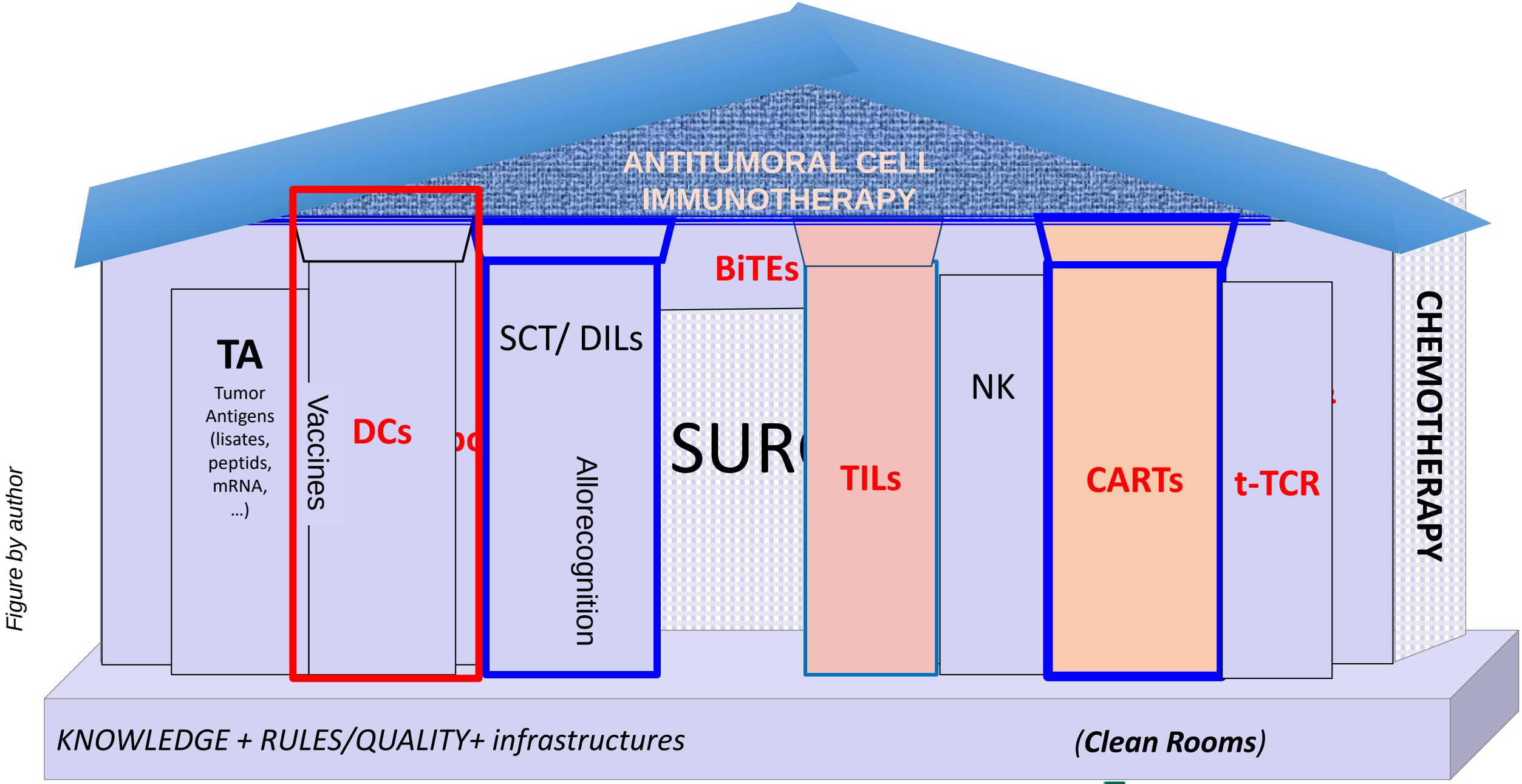
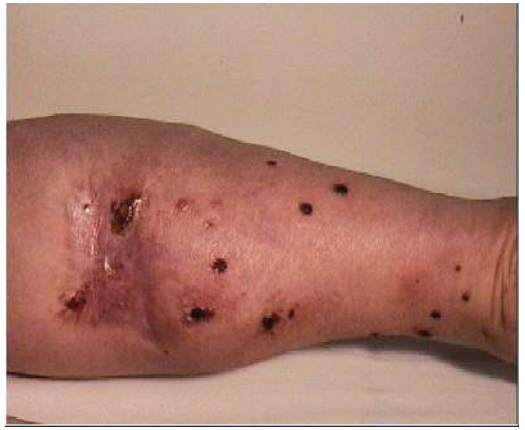


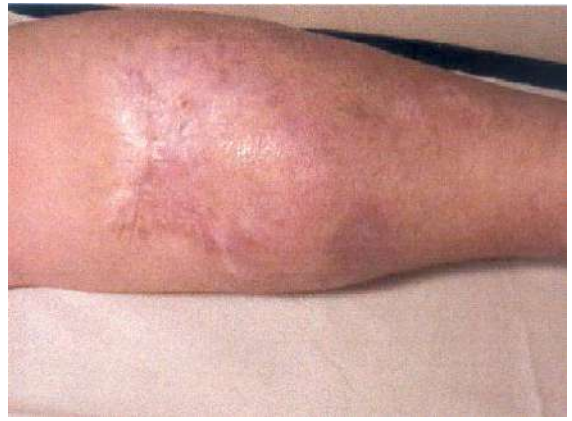
Figure by author

Cell Immunotherapy *(Dr. R Vilella)*:

Des de 1998: Vacuna anti-Melanoma
Des de 2004: DCs anti-Melanoma
Des de 2010: DCs anti-càncer de Colon

- Intradermal inoculations near the lymphatic areas.





Clinical results of the application of dendritic cells

	Clinical Response	Overall Survival
Melanoma	8.5 %	50 % - 377 %
Prostate Cancer	7.1 %	56 % - 175 %
Malignant Glioma	15.6 %	49 % - 150 %
Renal Carcinoma	11.5 %	108 %

>3000 patients

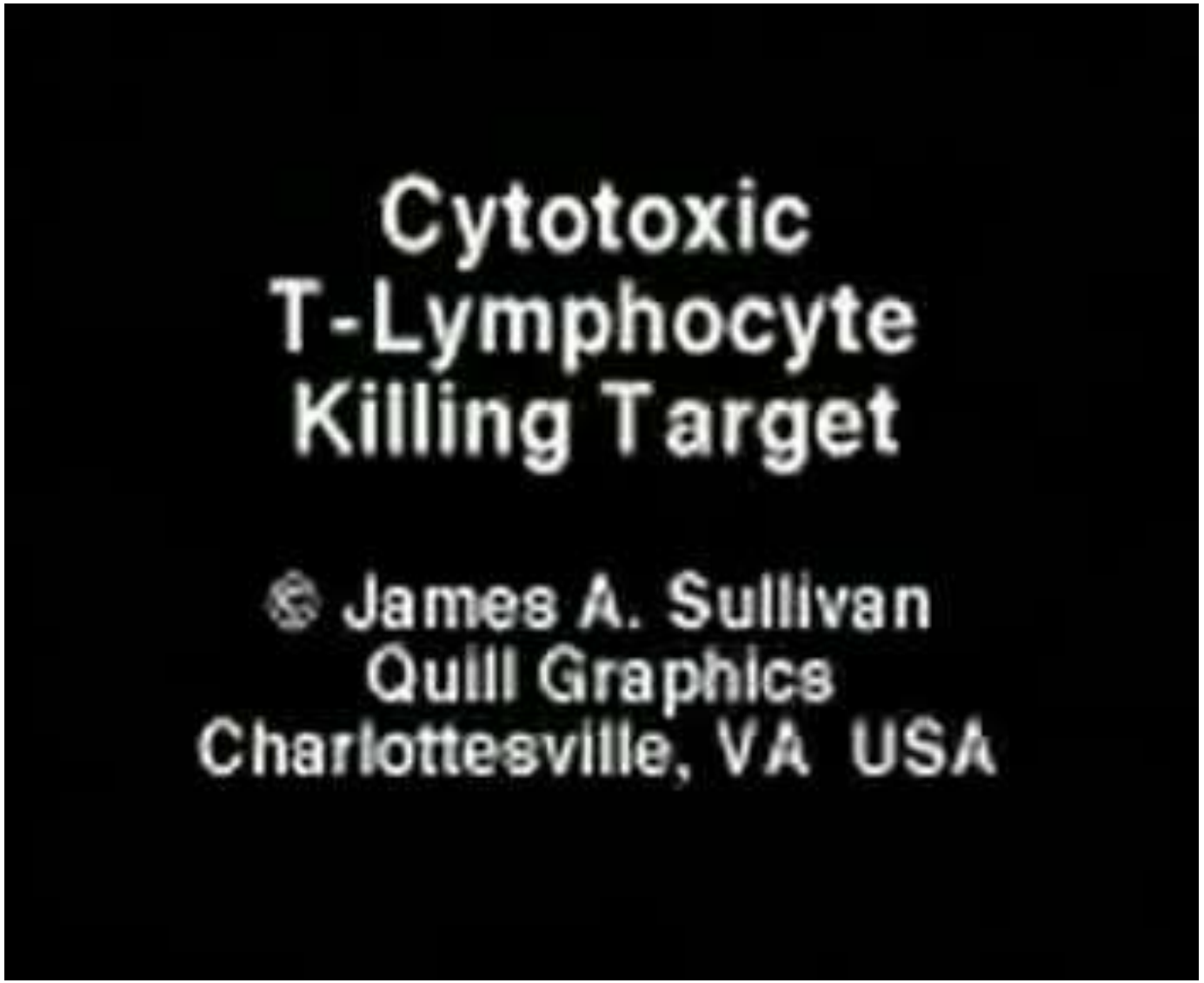
Data extracted from: Clinical use of dendritic cells for cancer therapy. Lancet Oncology 2014
Sébastien Anguille, Evelien L Smits, Eva Lion, Viggo F van Tendeloo, Zwi N Berneman

Ongoing clinical trials (based on the use of DCs) at Hospital Clinic de Barcelona

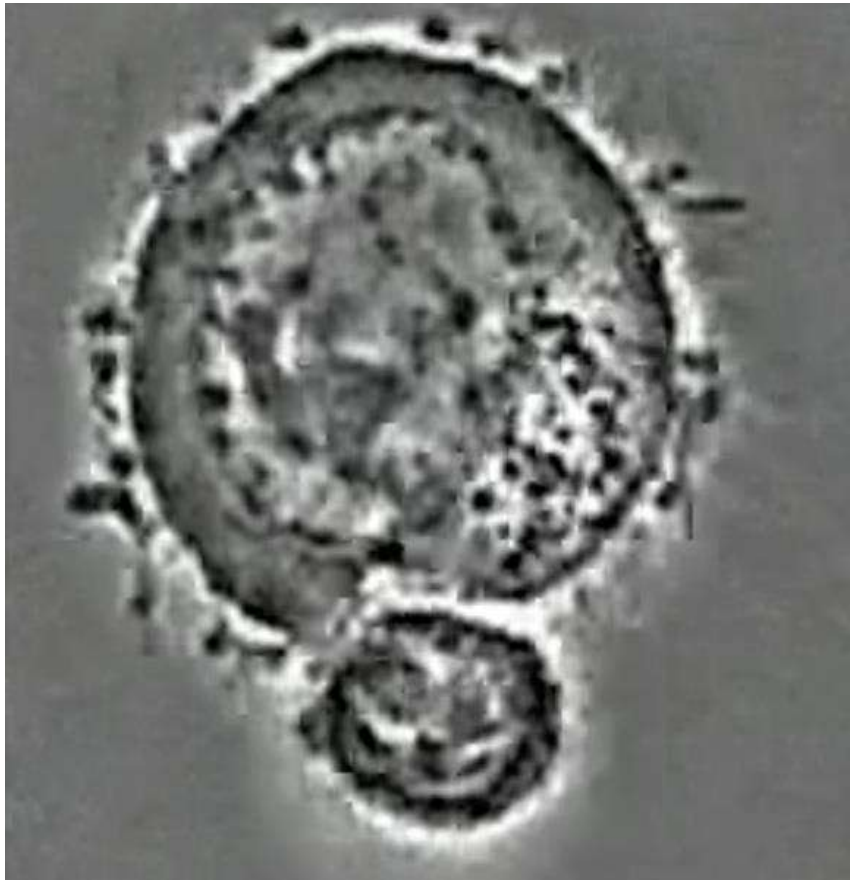
Protocol	PEI	NCT	Eudra-CT
Crohn intralesional	08-049	NCT02622763	2014-001083-35
MS*/NMO*	14-089	NCT02283671	2013-005165-39
DIPG*	15-215	NCT02840123	2015-003362-84
CCR* + anti-PD-L1	09-133	NCT01413295	2016-003838-24
SLC+ anti-PD-L1			2021-003154-66

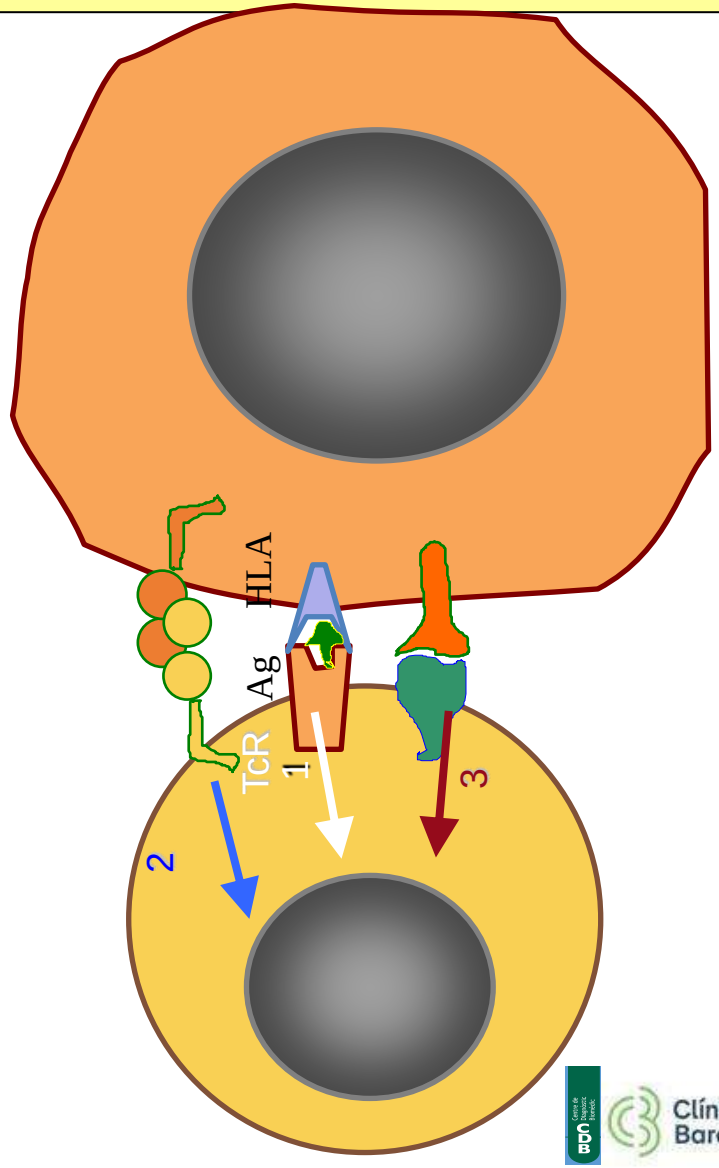
- MS/NMO: Multiple Sclerosis; neuromielitis optica
- **CCR**: Colo-rectal cancer + avelumab (Merck)
- **DIPG**: Difuse Intrinsec Pontine Glioma (Pediatric)
- **SCLC**: Small Cell Lung Cancer

T-cell Cytotoxicity

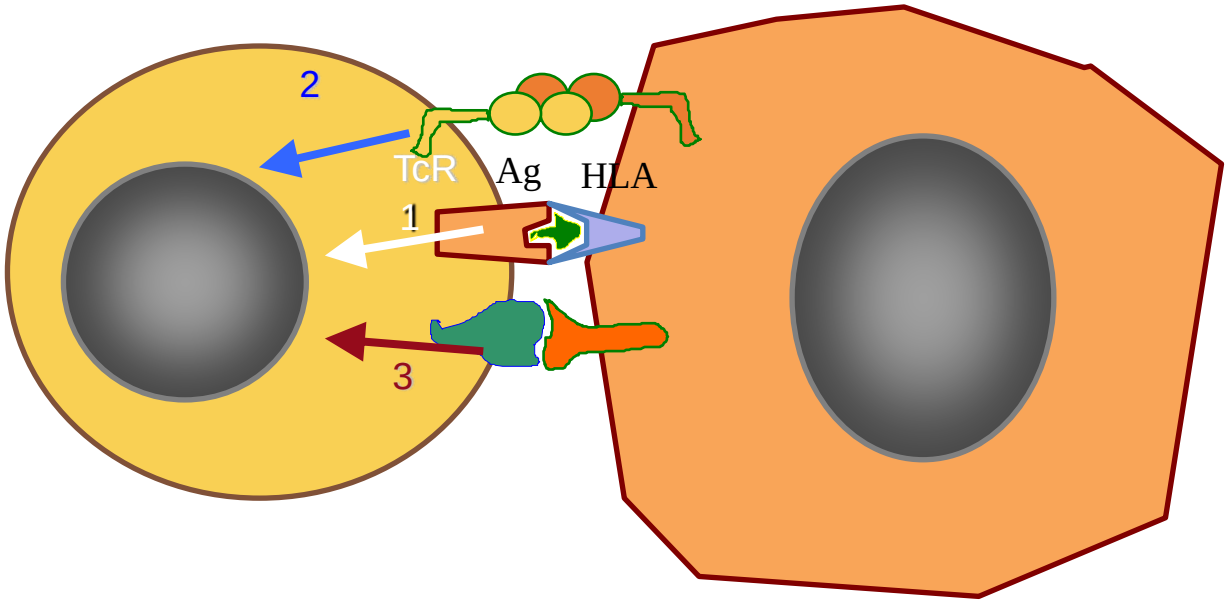


T-cell Cytoxicity: TA recognition & more

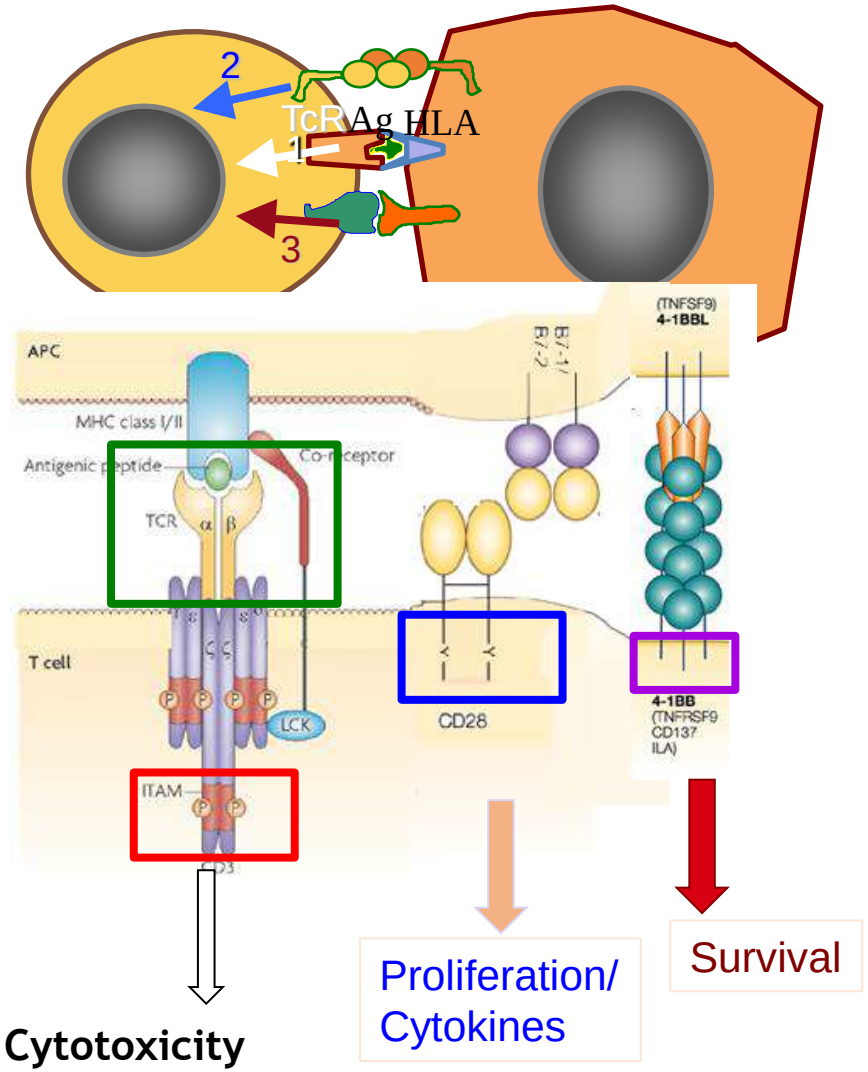




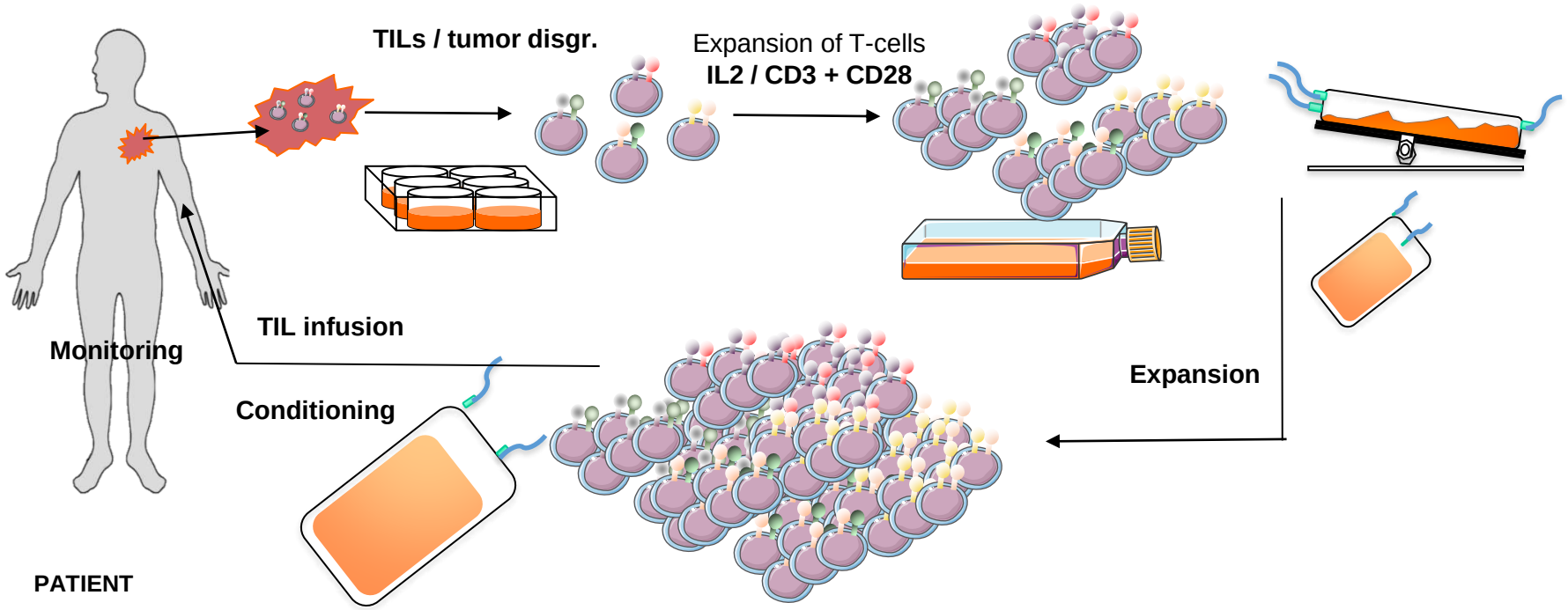
T-cell Cytoxicity: TA recognition & more



T-cell Cytoxicity: TA recognition & more

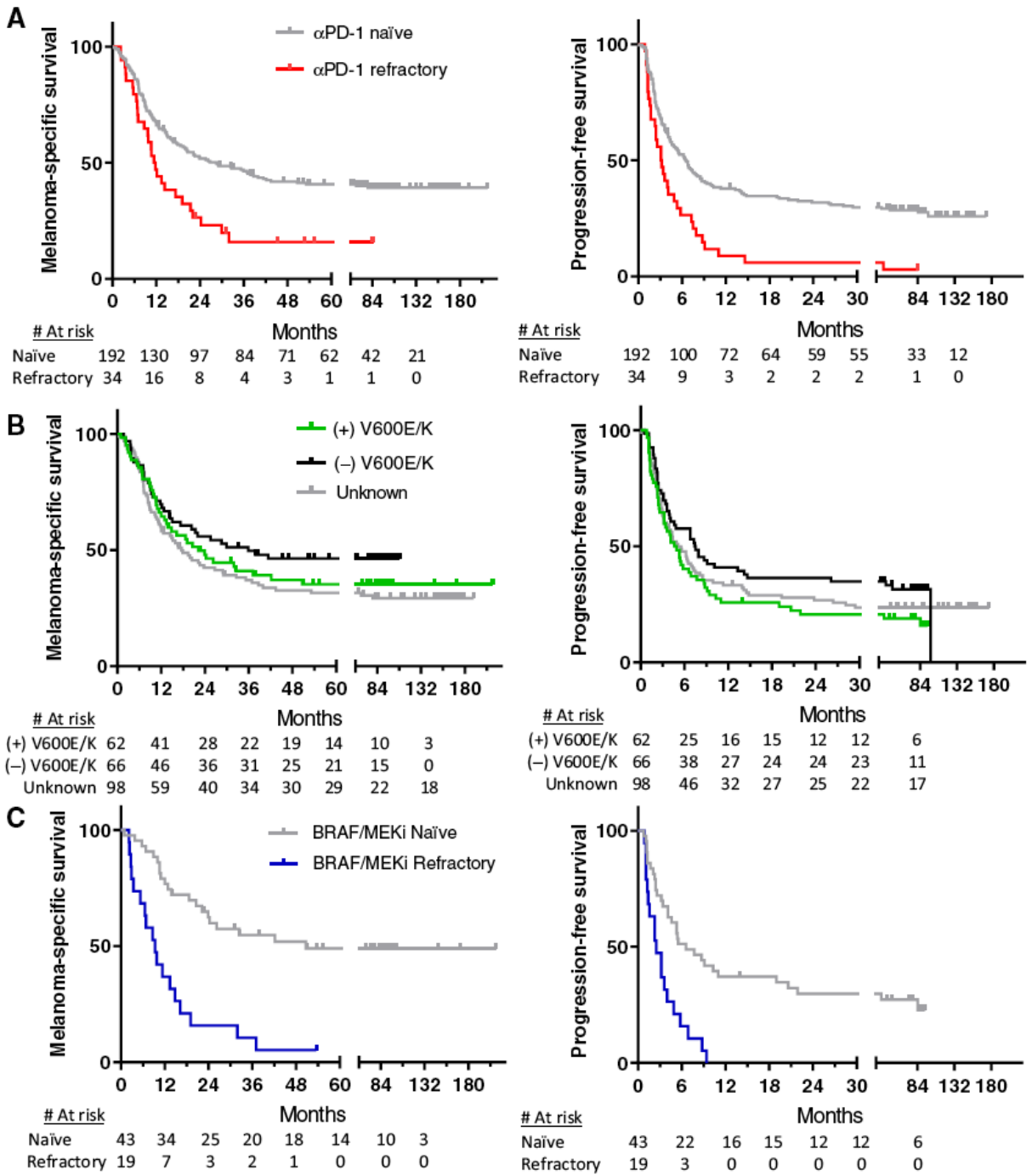


TILs



UNDER **GMP** CONDITIONS

Figure made by the speaker.
TILs, tumour infiltrating lymphocytes.



Impact of Prior Treatment on the Efficacy of Adoptive Transfer of Tumor-Infiltrating Lymphocytes in Patients with Metastatic Melanoma

Seitter SJ et al.
Clin Cancer Res
2021;27:5289–98

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2022 VOL. 387 NO. 23

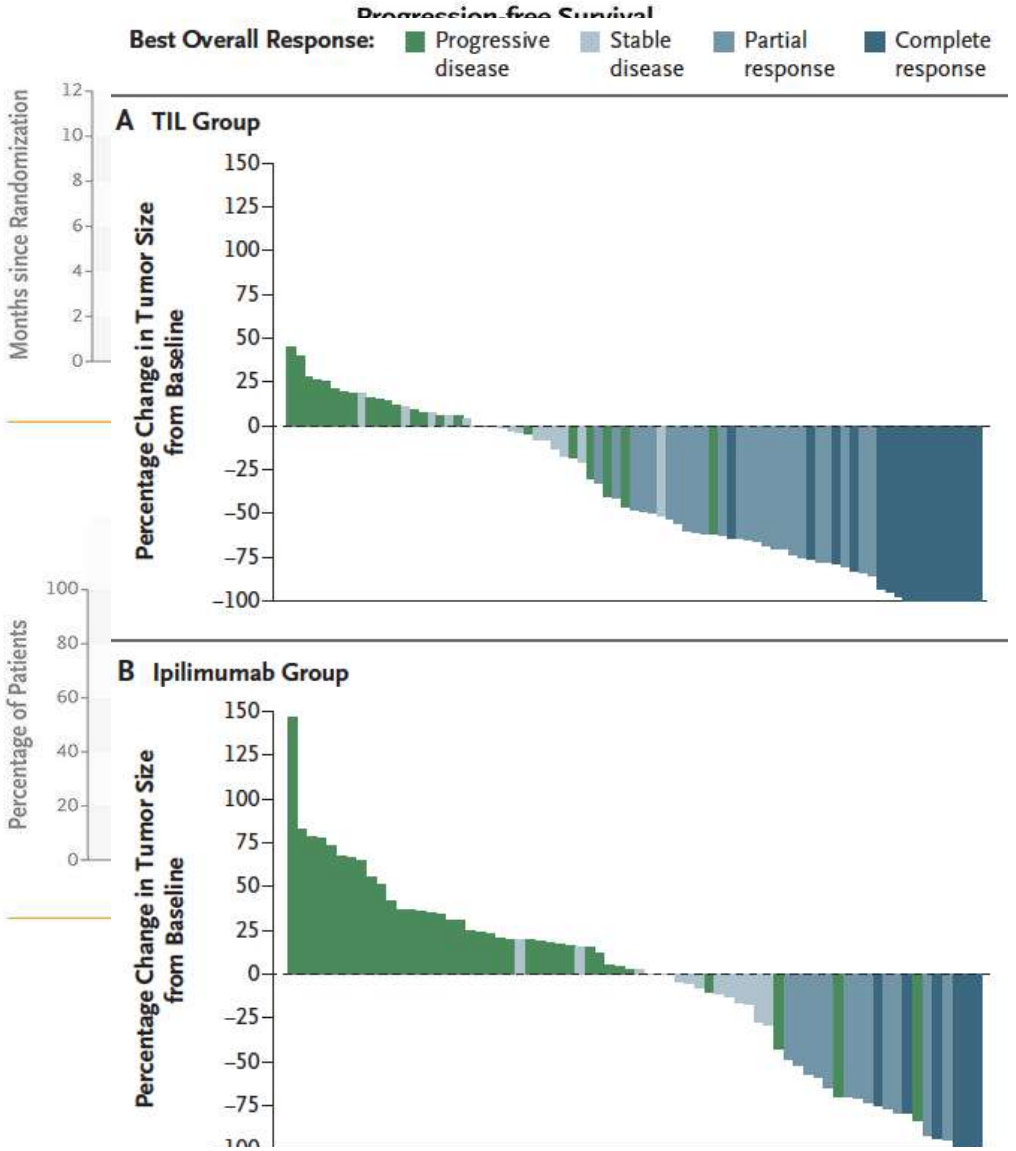
Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

M.W. Rohaan, T.H. Borch, J.H. van den Berg, Ö. Met, R. Kessels, M.H. Geukes Foppen, J. Stoltenborg Granhøj, B. Nuijen, C. Nijenhuis, I. Jedema, M. van Zon, S. Scheij, J.H. Beijnen, M. Hansen, C. Voermans, I.M. Noringriis, T.J. Monberg, R.B. Holmstroem, L.D.V. Wever, M. van Dijk, L.G. Grijpink-Ongering, L.H.M. Valkenet, A. Torres Acosta, M. Karger, J.S.W. Borgers, R.M.T. ten Ham, V.P. Retèl, W.H. van Harten, F. Lalezari, H. van Tinteren, A.A.M. van der Veldt, G.A.P. Hospers, M.A.M. Stevense-den Boer, K.P.M. Suijkerbuijk, M.J.B. Aarts, D. Piersma, A.J.M. van den Eertwegh, J.-W.B. de Groot, G. Vreugdenhil, E. Kapiteijn, M.J. Boers-Sonderen, W.E. Fiets, F.W.P.J. van den Berkmortel, E. Ellebaek, L.R. Hölmich, A.C.J. van Akkooi, W.J. van Houdt, M.W.J.M. Wouters, J.V. van Thienen, C.U. Blank, A. Meerveld-Eggink, S. Klobuch, S. Wilgenhof, T.N. Schumacher, M. Donia, I.M. Svane, and J.B.A.G. Haanen

EDITORIALS

TIL Therapy Entering the Mainstream

George Coukos, M.D., Ph.D.



"… response in **49% of the patients** with melanoma who received **TILs** (most of whom had previously received anti–PD-1 therapy), as **compared with** a response in **21%** of the patients who received **ipilimumab**, findings that show the clear **superiority of TIL therapy over** … (**CTLA-4**) **blockade** as second-line treatment. Both multicenter investigations show that TIL therapy **can no longer be considered a "boutique" treatment** and is entering the mainstream.

ACT -> durable responses in solid tumors

	N	ORR	DoR months
MELANOMA (Rosenberg; CCR, 2011)	43	49%	82+,81+, 79+, 78+, 64+
MELANOMA (Rosenberg;CCR, 2011)	25	52%	68+, 64+, 60+, 57+, 54+
MELANOMA (Rosenberg; CCR, 2011)	25	72%	48+, 45+, 44+, 44+, 39+, 38+, 37+, 19+, 20, 22
MELANOMA (Besser; CCR, 2010)	20	50%	20+, 4+
MELANOMA (Ellebaek; JTM, 2012)	6	33%	30+, 10+
UVEAL MELANOMA (Chandranl; Lancet Oncol, 2017)	20	35%	21+

18% with complete response (25/139)
18 pts with maintained response after 2 years

	N	ORR	DoR months
Unselected ACT			
OVARIAN CANCER (Pedersen; OncoImmunology, 2018)	6	0%	NA
CERVICAL CANCER (Jazaeri AAl; ASCO 2019)	27	44%	Not reached 2.6+ to 9.2+
Selective ACT			
CHOLANGIOCA (Tran; Science, 2014)	1	PR	35
COLORECTAL (Tran; NEJM, 2016)	1	PR	9
BREAST CANCER (Zacharakis; Nature med, 2018)	1	CR	22+

MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS DE USO HUMANO

Área de Ensayos Clínicos

ASUNTO: **Respuesta a Condiciones en la Resolución de Autorización** 2020-003638-19

DESTINATARIO: CTU CLINIC
Villarroel 170
08036 Barcelona

PROMOTOR: Fundació Clínic per a la Recerca Biomèdica
Rosselló 149-153
08036 Barcelona

En relación con las respuestas recibidas en fecha 11 de Julio de 2022 para las condiciones de la Resolución de Autorización del ensayo clínico titulado:

Tratamiento de cáncer de mama triple negativo avanzado o metastásico con terapia adoptiva de linfocitos infiltrantes de tumor PD1 positivo.

Tras evaluar la respuesta a las condiciones de autorización de este ensayo, **la AEMPS comunica que está conforme con las mismas**.

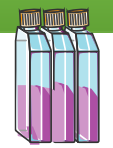
JEFE DE DEPARTAMENTO DE MEDICAMENTOS DE USO HUMANO

agencia española de medicamentos y productos sanitarios

Cesar Hernández García

t

Phase 3:
Production of the "active substance" ("ATMP")



(i) & (ii) REP (*Rapid expansion protocol)*

+ IL-2, anti-CD3, *feeder cells*

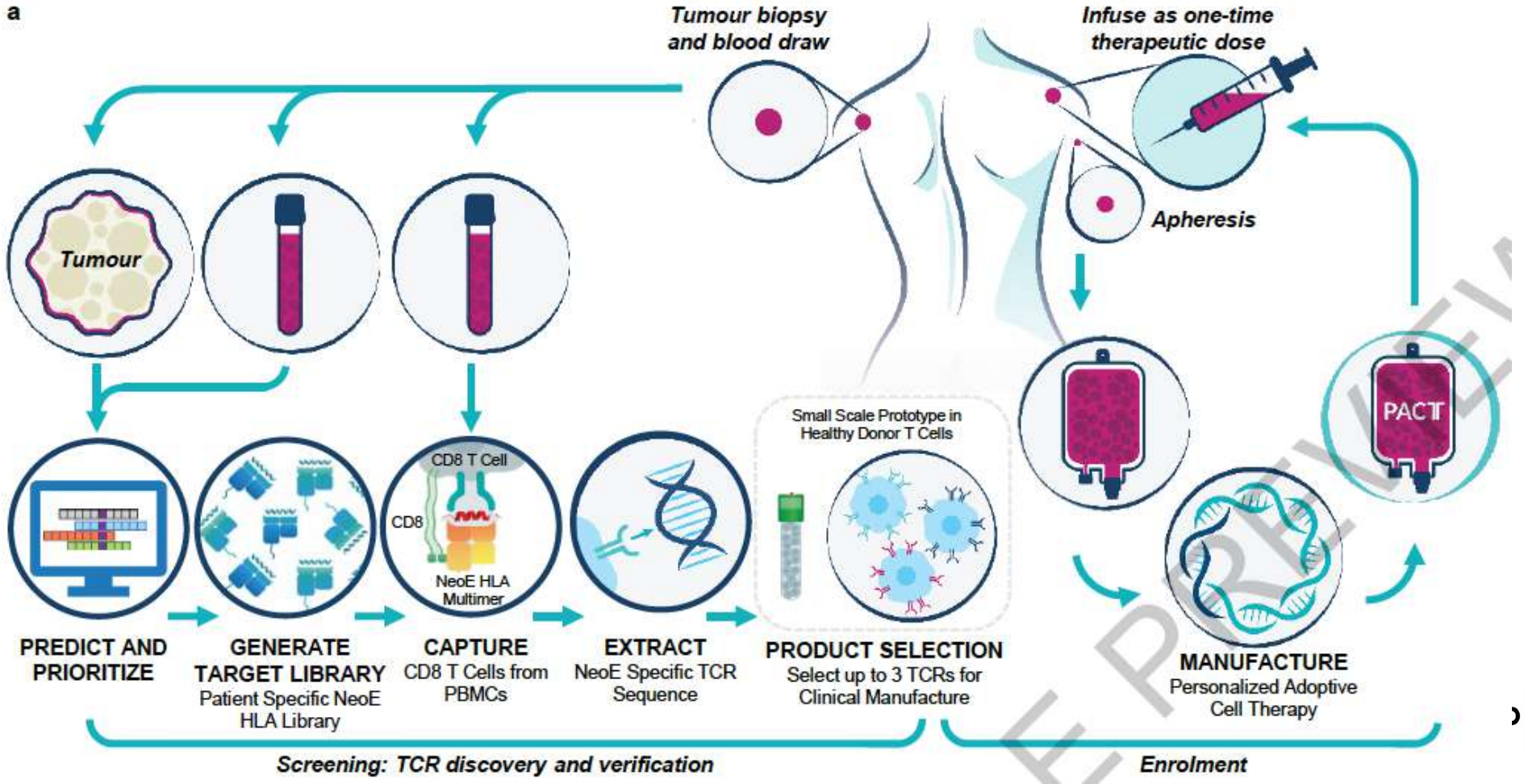
n of TILs
)3+ PD1+

nature

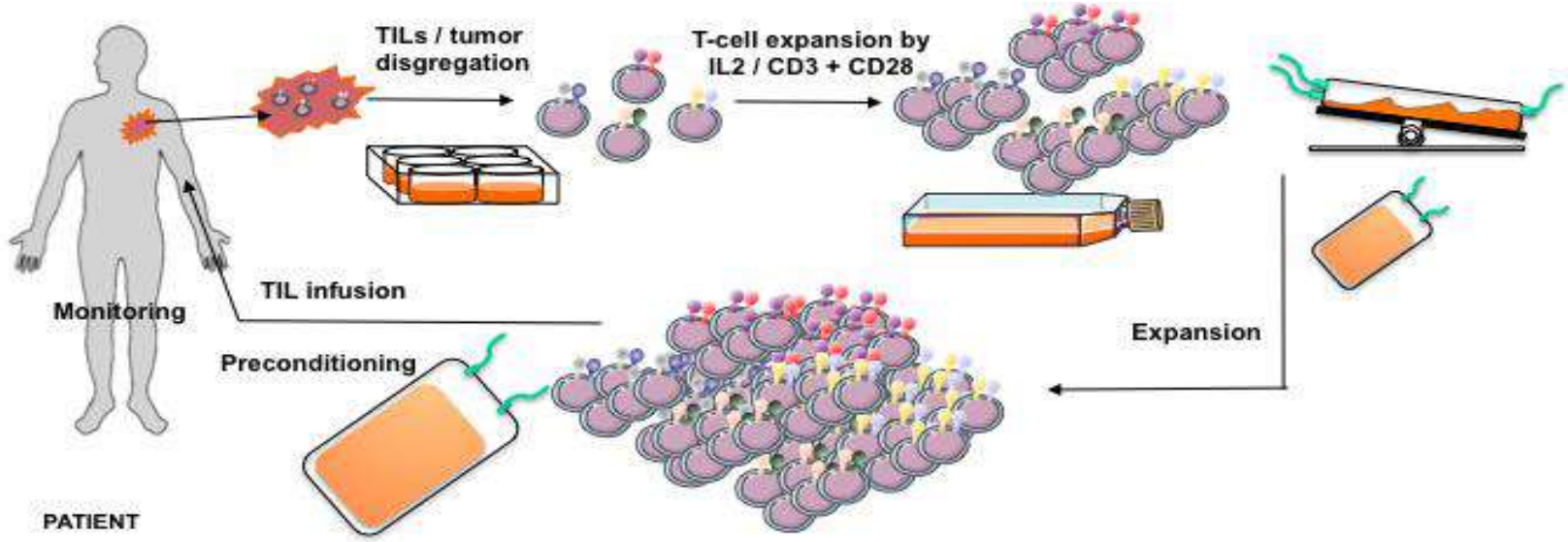
https://doi.org/10.1038/s41586-022-05531-1

Accelerated Article Preview

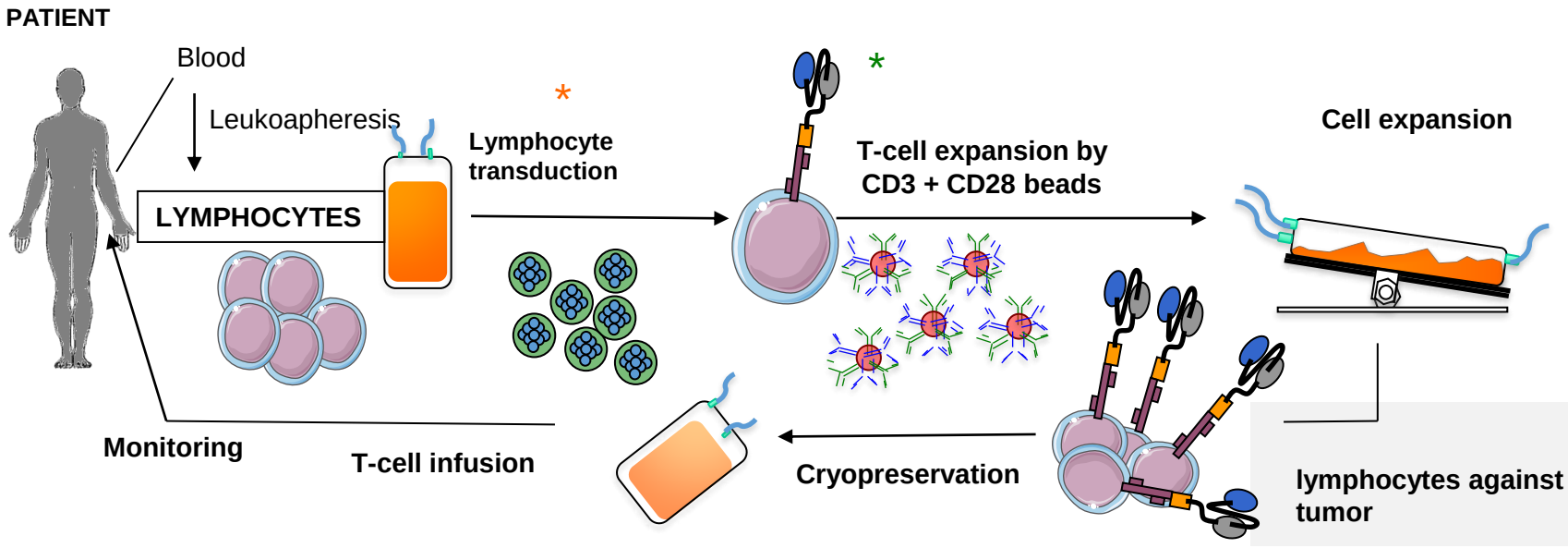
Non-viral precision T cell receptor replacement for personalized cell therapy



From TILs to T-cell modified therapy



UNDER GMP CONDITIONS



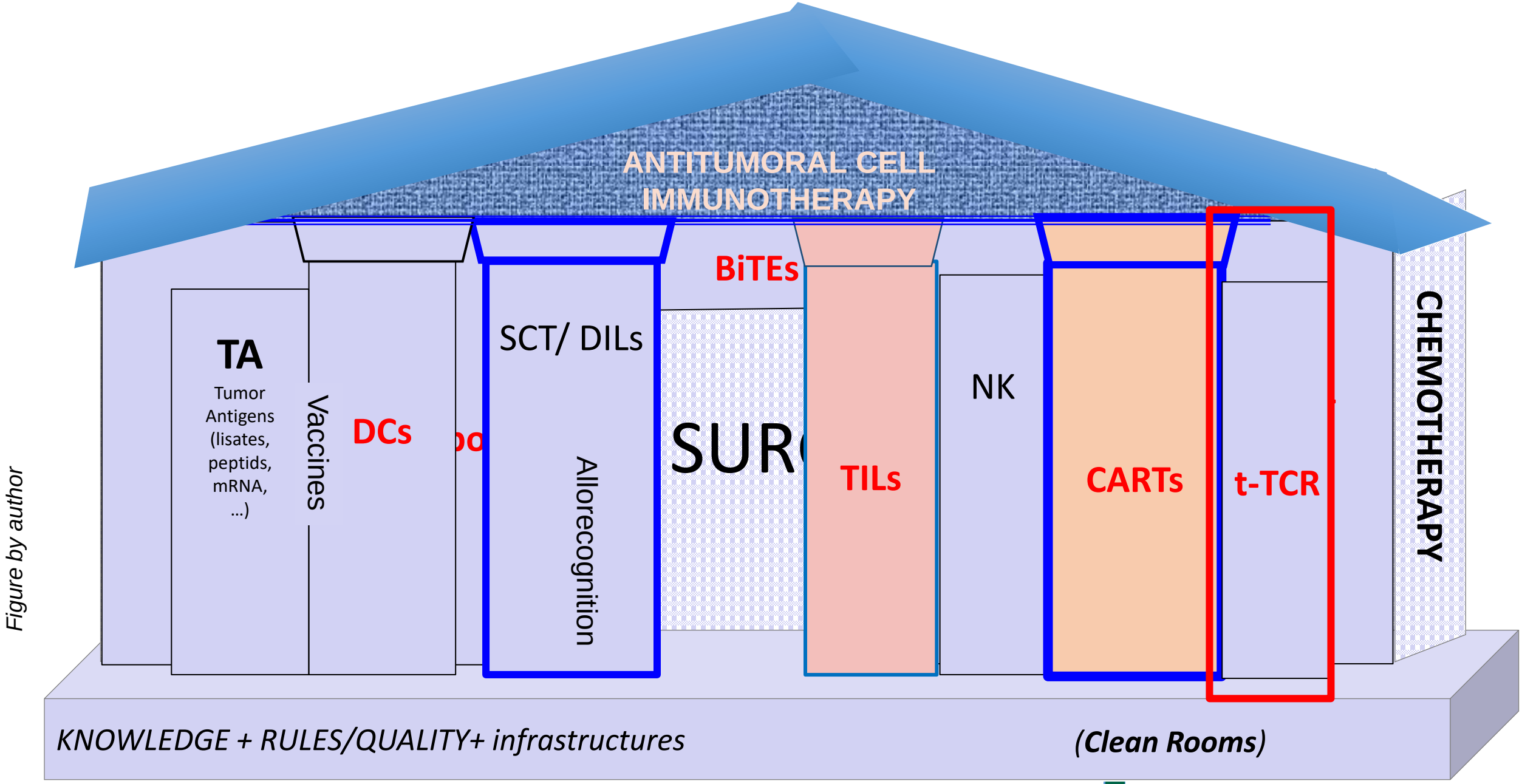
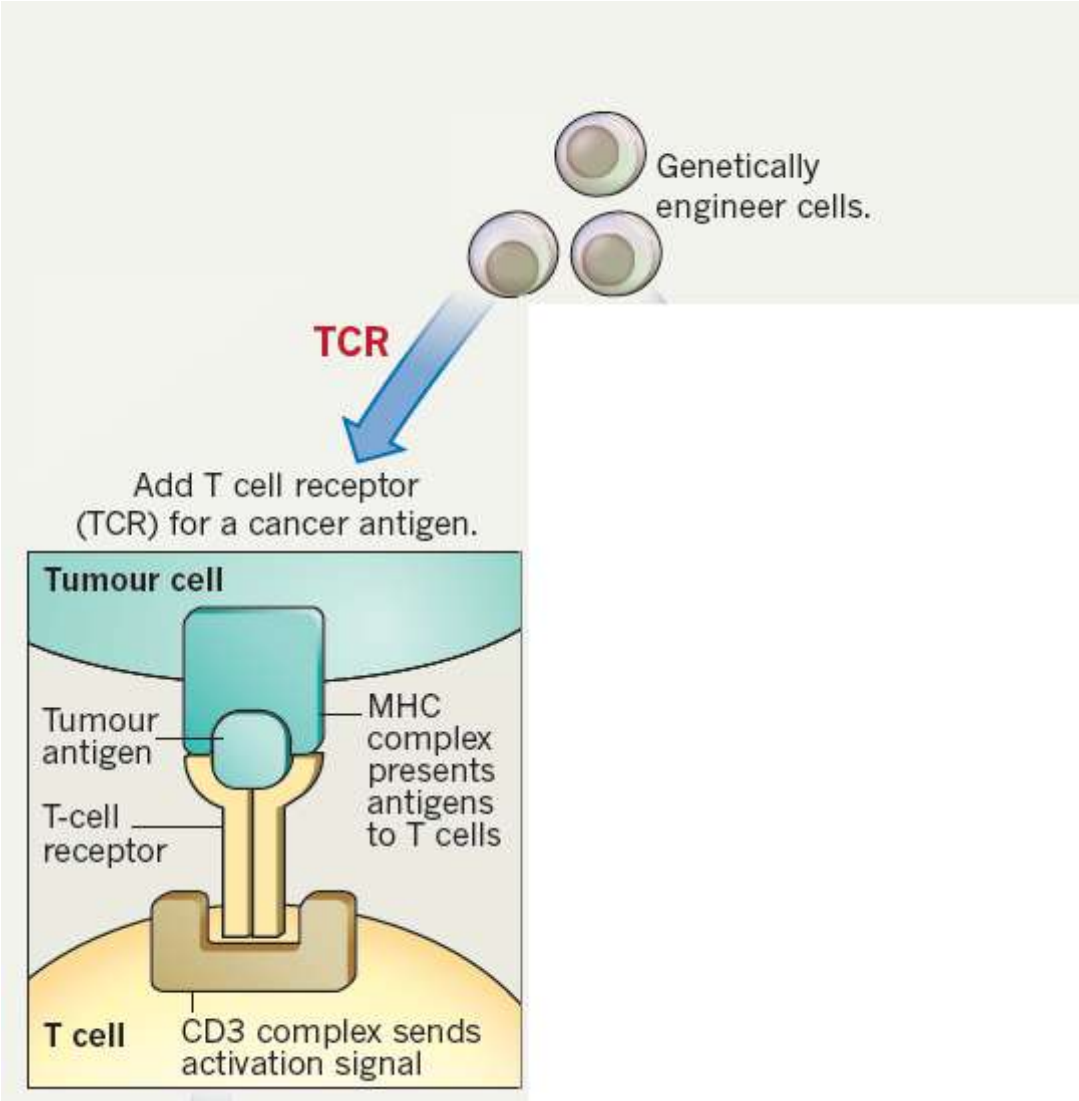
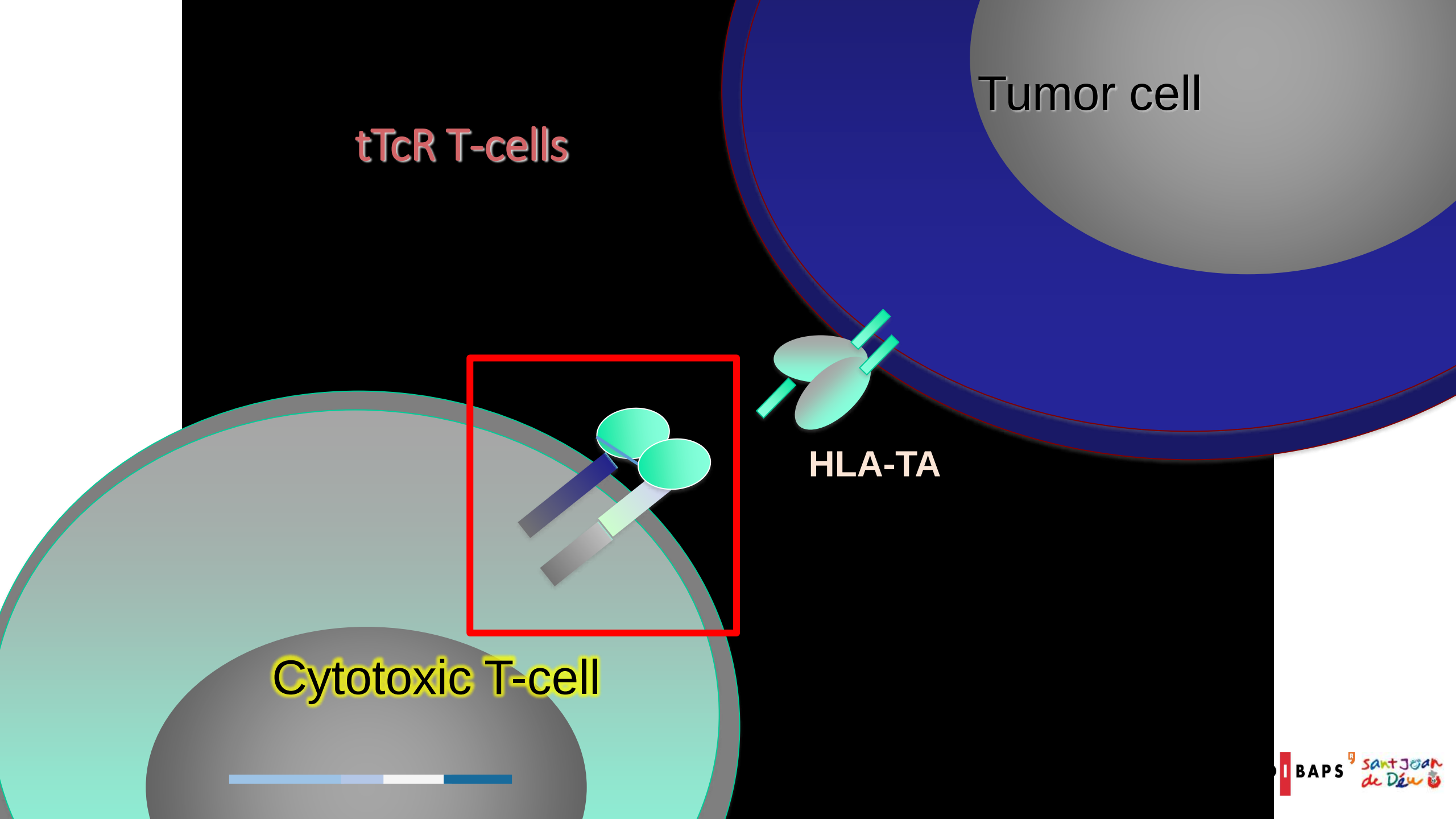


Figure by author

Ex vivo modification of T-cell



Humphries C, Nature 504, S13-S15 2013


tTcR T-cells
Tumor cell
HLA-TA
Cytotoxic T-cell

Target	Trial number	Study period (Status)	Patient no (est.)	Vector/mode	HLA allele	Cancer targeted
MART-1	NCT00509288	2007-2011 (C)	24	Retroviral vector	HLA-A*0201	Metastatic cutaneous melanoma[2]
	NCT00612222	2008-2011 (T)	4	Retroviral vector + ALVAC vaccine	HLA-A*0201	Metastatic cutaneous melanoma
	NCT00910650	2009-2019 (C)	14	+ dendritic cell vaccine	HLA-A*0201	Metastatic cutaneous melanoma[3]
	NCT02654821	2012-2019 (A, nr)	12 (25)	Retroviral vector	HLA-A*0201	Metastatic cutaneous and uveal melanoma
MART-1 gp 100	NCT00923195	2008-2011 (C)	4 (85)	Retroviral vector + peptide vaccine	HLA-A*0201	Metastatic cutaneous melanoma[4]
gp100	NCT00610311	2008-2011 (T)	3	+ ALVAC vaccine murine TCR	HLA-A*0201	Metastatic cutaneous melanoma
	NCT00509496	2007-2011 (T)	21	Retroviral vector	HLA-A*0201	Metastatic cutaneous melanoma
NY-ESO-1	NCT00670748	2008-2016 (T)	45	Retroviral vector	HLA-A*0201	Metastatic cancers, melanoma/RCC and others[5]
	NCT01457131	2011-2013 (T)	2	Retroviral vector w/inducible IL-12	HLA-A*02:01	Metastatic cancers, melanoma and others
	NCT01350401	2011-2016 (T)	4	Lentiviral vector enhanced TCR	HLA-A*0201	Metastatic, cutaneous melanoma
	NCT01967823	2013-2020 (C)	11	Retroviral vector murine TCR	HLA-A*02:01	Metastatic cancers, melanoma and others
	NCT02062359	2014-2016 (T)	2	Retroviral vector CD62L+ T cells	HLA-A*0201	Metastatic cutaneous melanoma
	NCT02366546	2015-2018 (A, nr)	9[1]	Unknown	HLA-A*02:01 HLA-A*02:06	Metastatic cancers, melanoma and others
	NCT02457650	2015-2019 (R)	36[1]	Unknown	HLA-A*02:01	NY-ESO-1 + malignancies (children and adult)
	NCT02869217	2016-2020 (A, nr)	22[1]	Unknown	HLA-A*02:01 HLA-A*02:06	Metastatic cancers, melanoma and others
	NCT03638206	2018-2023 (R)	73[1] (incl. CAR-T trial)	Unknown	HLA-A*02:01	Metastatic cancers, melanoma and others incl. multiple myeloma
	NCT03399448	2018-2033 (A, nr)	3[1]	Lentiviral vector CRISPR TCRendo and PD-1	HLA-A*02:01	Metastatic cancers, melanoma and others
MAGE						
A3/12	NCT01273181	2010-2012 (T)	9 (97)	Retroviral vector	HLA-A*0201	Metastatic cancers, melanoma and RCC[6]
A3	NCT02153905	2014-2018 (T)	3 (102)	Retroviral vector	HLA-A*01	Metastatic cancers, melanoma and others
A3	NCT02111850	2014-2023 (R)	17[1] (107)	Retroviral vector CD4 TCR	HLA-DP4	Metastatic cancers, melanoma and others[7]
A4	NCT01694472	2012-2016 (U)	15[1]	Unknown	HLA-A*24:02	Metastatic cancers, melanoma and others
A4	NCT03132922	2017-2020 (R)	42[1]	Lentiviral vector	HLA-A*02	Metastatic cancers, melanoma and others
A10	NCT02989064	2016-2019 (A, nr)	22[1]	Lentiviral vector	HLA-A*02:01 HLA-A*02:06	Metastatic cancers, melanoma and others
A1	NCT03441100	2019-2020 (R)	(16)[1]	Viral vector IMA202	Unknown	Metastatic cancers, melanoma and others
PRAME	NCT02743611	2017-2019 (A, nr)	28 (36)	Rimiducid-inducible safety switch	HLA-A*02:01	Metastatic uveal melanoma, relapsed AML and MDS
	NCT03686124	2019-2021 (R)	(16)	Viral vector IMA203	Unknown	Metastatic cancers, melanoma and others
p53	NCT00393029	2006-2008 (C)	12	Retroviral vector	HLA-A*02:01	Metastatic cancers, melanoma and others
	NCT00704938	2008-2009 (T)	3 (82)	+dendritic cell vaccine	HLA-A*0201	Metastatic cancer, melanoma/RCC and others
Tyrosinase	NCT01586403	2012-2028 (A, nr)	3(14)[1]	Retroviral vector	HLA-A*02	Metastatic melanoma[8]
Neoantigens	NCT03970382	2019 - (R)	(148)	CD8 and CD4 TCR ± nivolumab	Unknown	Metastatic cancers, melanoma and others

Note: All clinical studies using TCR therapy against malignant melanoma registered on ClinicalTrials.gov. [1]No updated information on enrolment available; [2]Ref 102; [3]Ref 103; [4]Ref 102; [5]Ref 104; [6]Ref 77; [7]Ref 105; [8]Ref 53.
Abbreviations: (A, nr), Active, not recruiting; (C), Completed; (R), Recruiting; (T), Terminated; (U), Unknown.

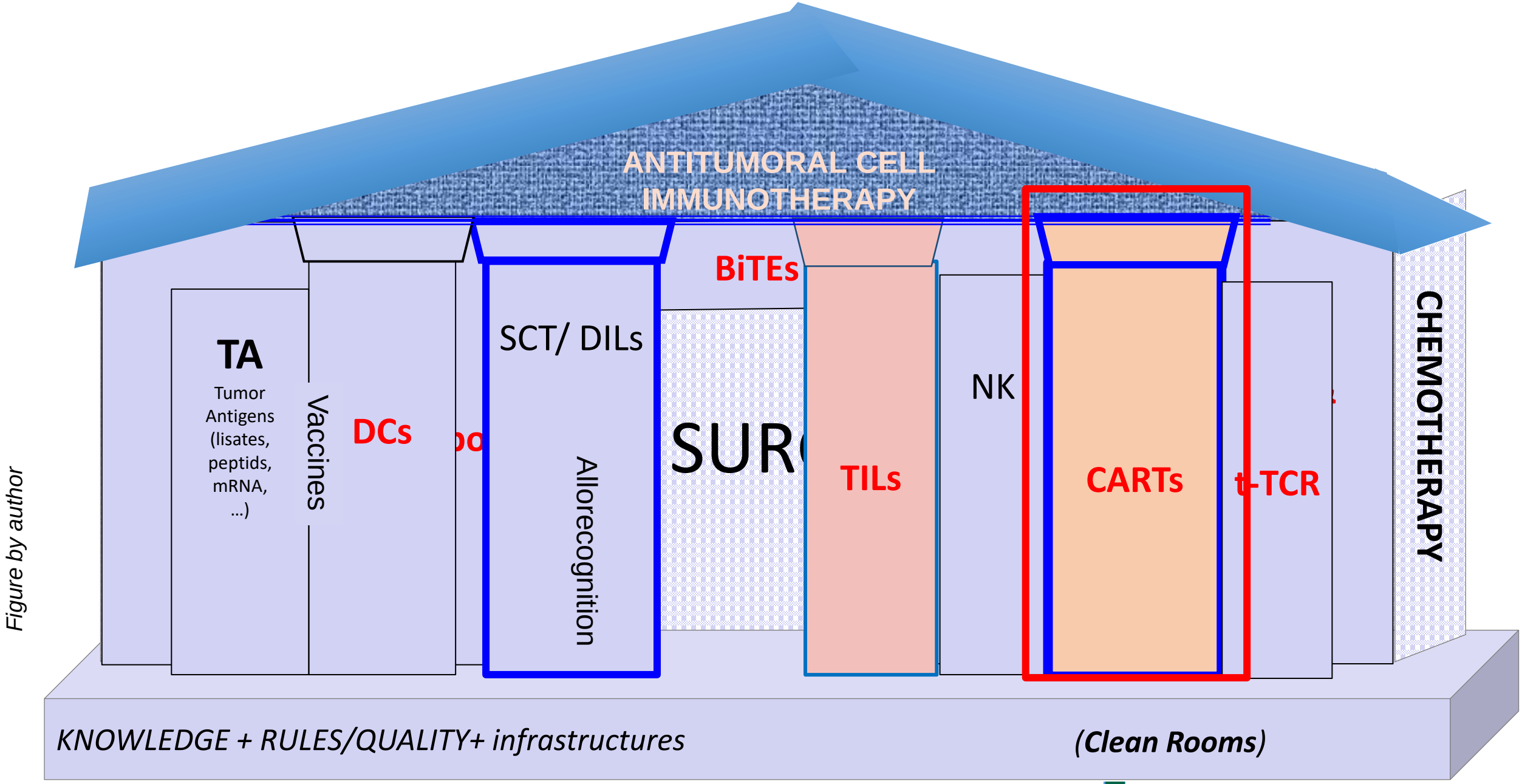
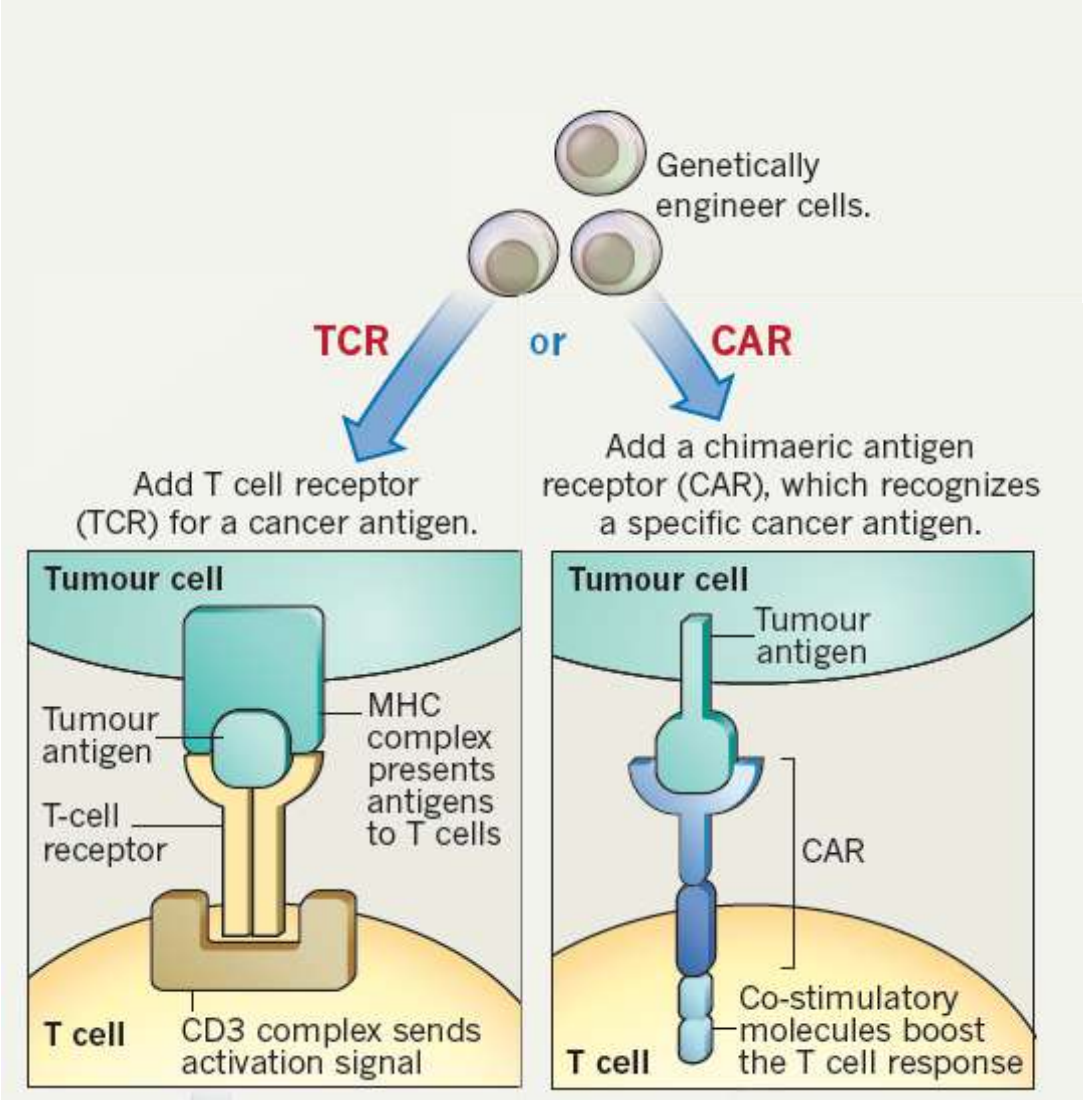


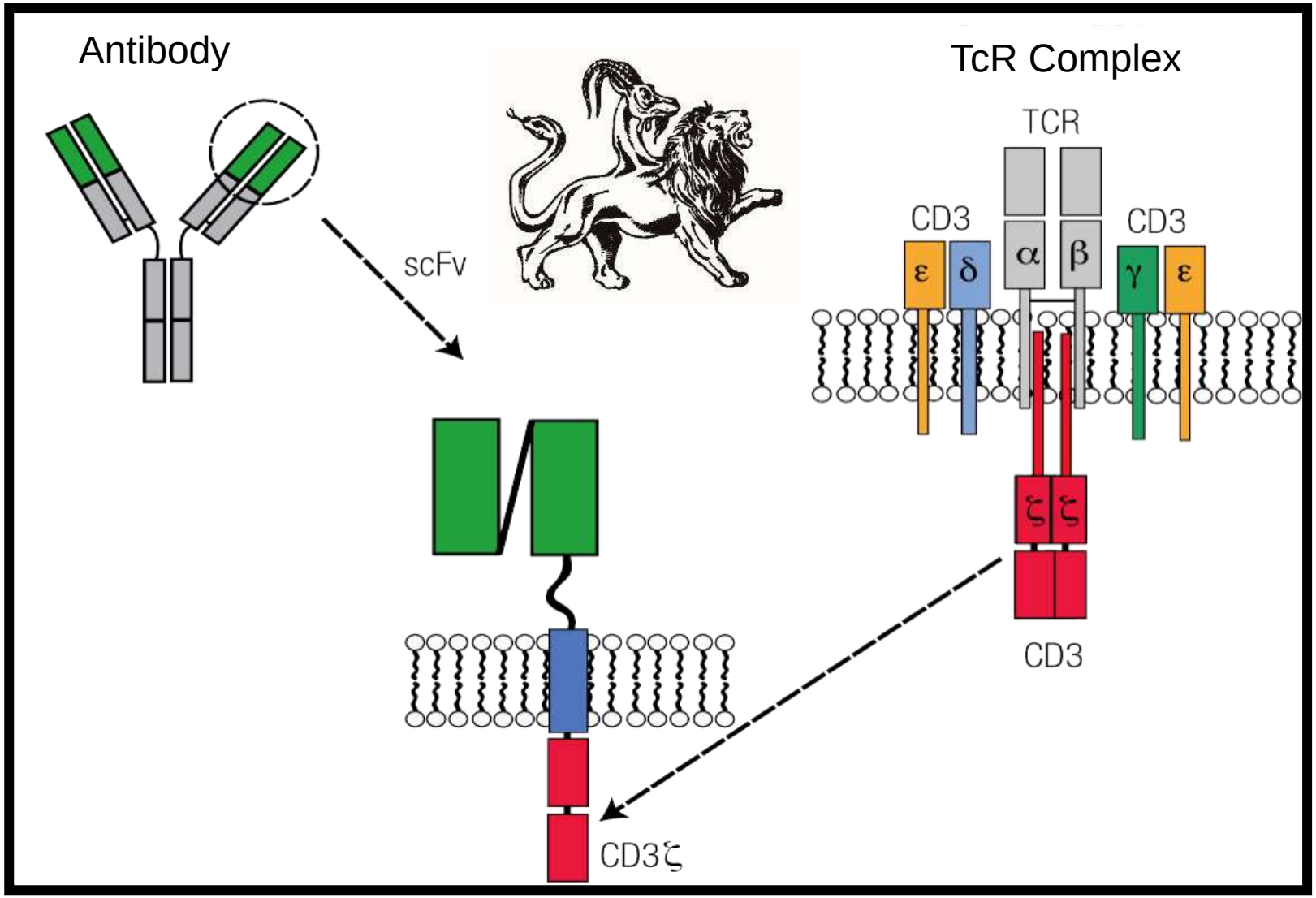
Figure by author

Ex vivo modification of T-cell

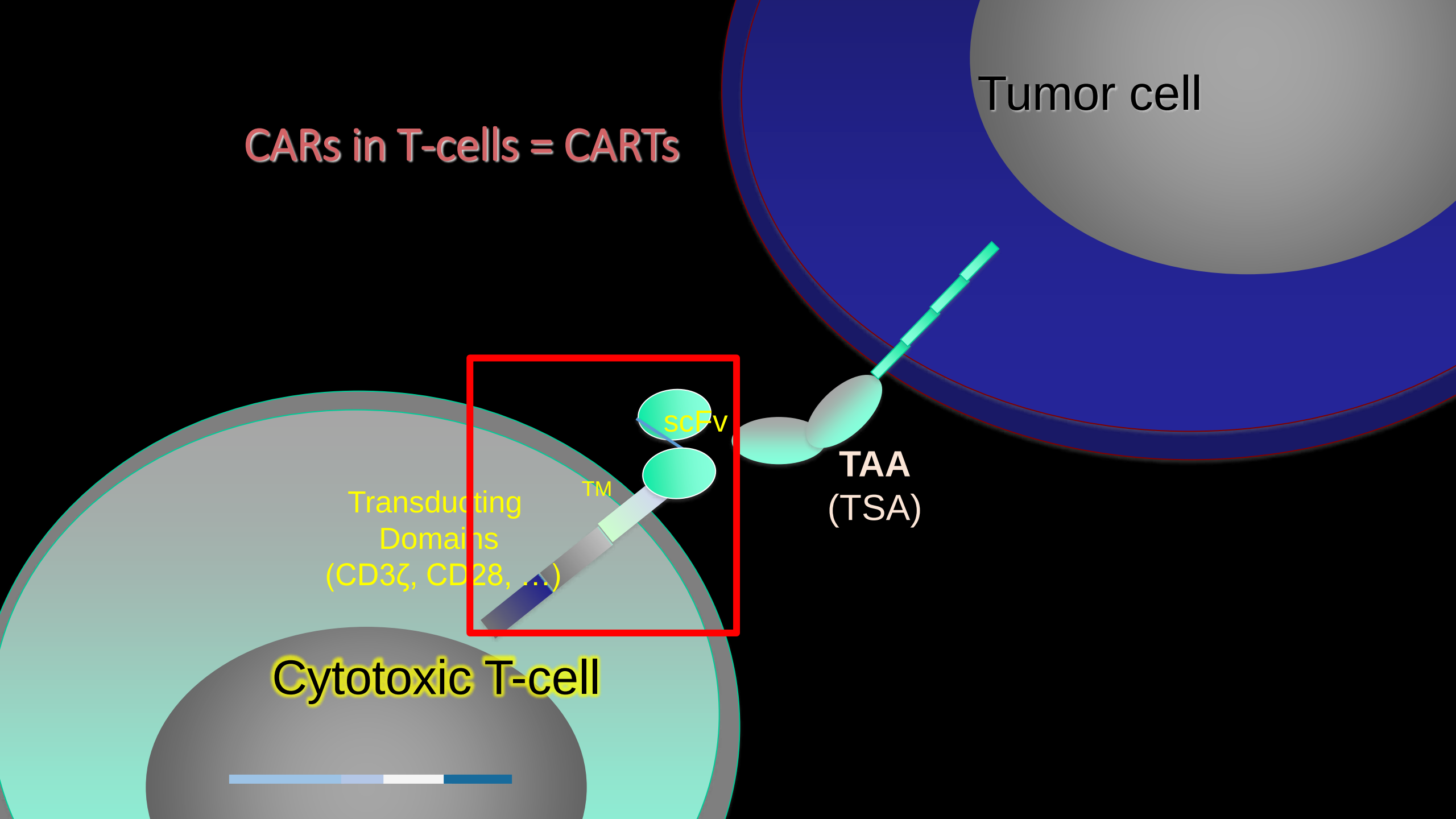


Humphries C, Nature 504, S13-S15 2013

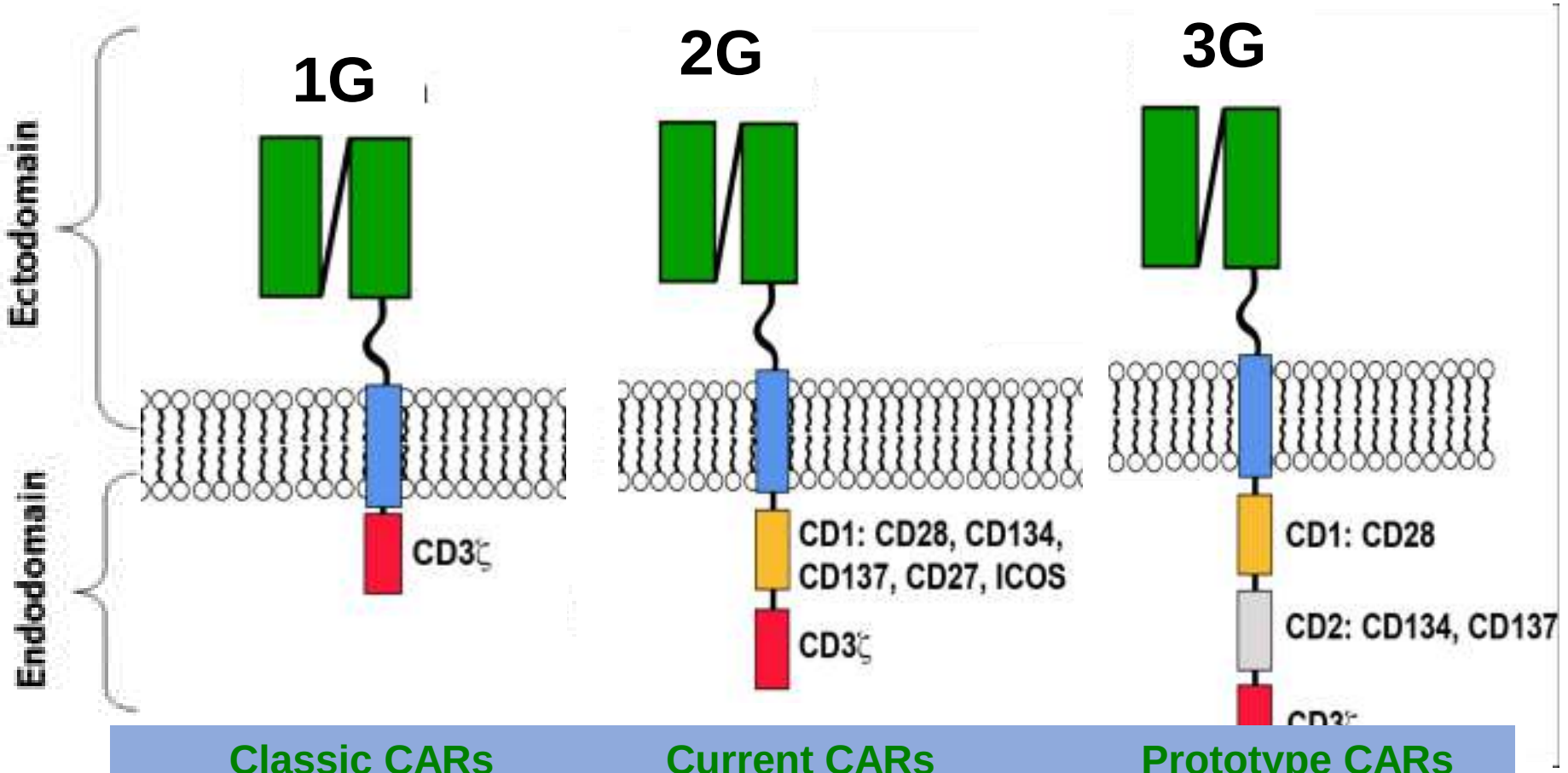
CAR = *Chimeric Antigen Receptor*



CARs in T-cells = CARTs

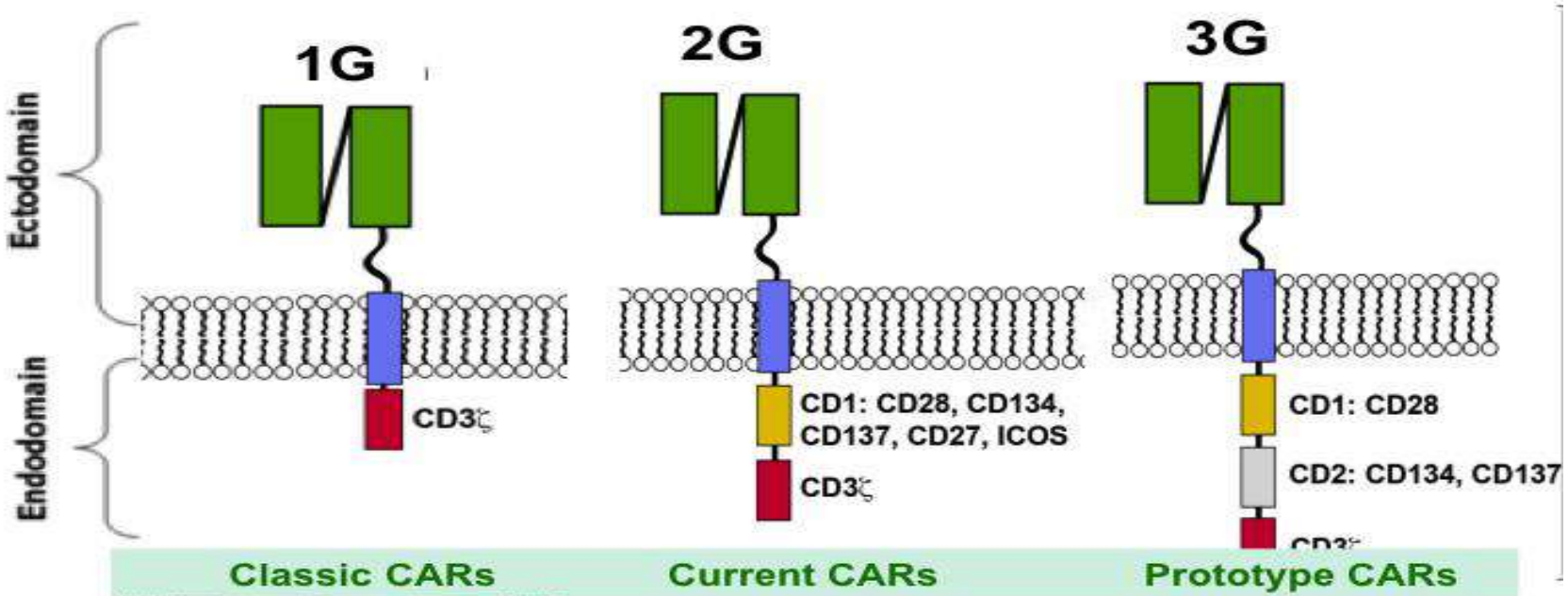


CAR evolution



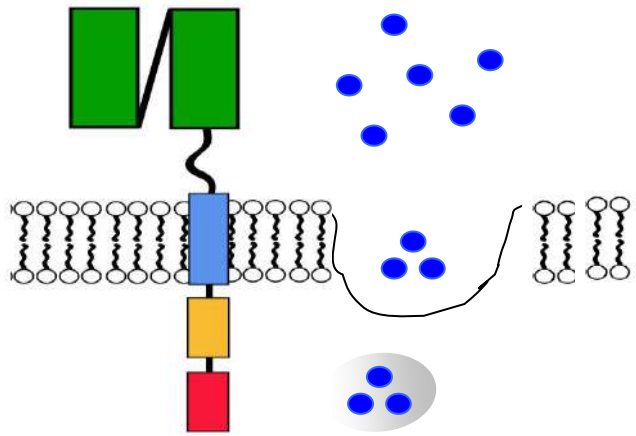
Capítulo 6. Monografías SEI – Elsevier. “Inmunoterapia antitumoral con linfocitos genéticamente modificados (CAR): una realidad con futuro”

CAR evolution



Capitulo 6. Monografías SEI – Elsevier. "Inmunoterapia antitumoral con linfocitos genéticamente modificados (CAR): una realidad con futuro"

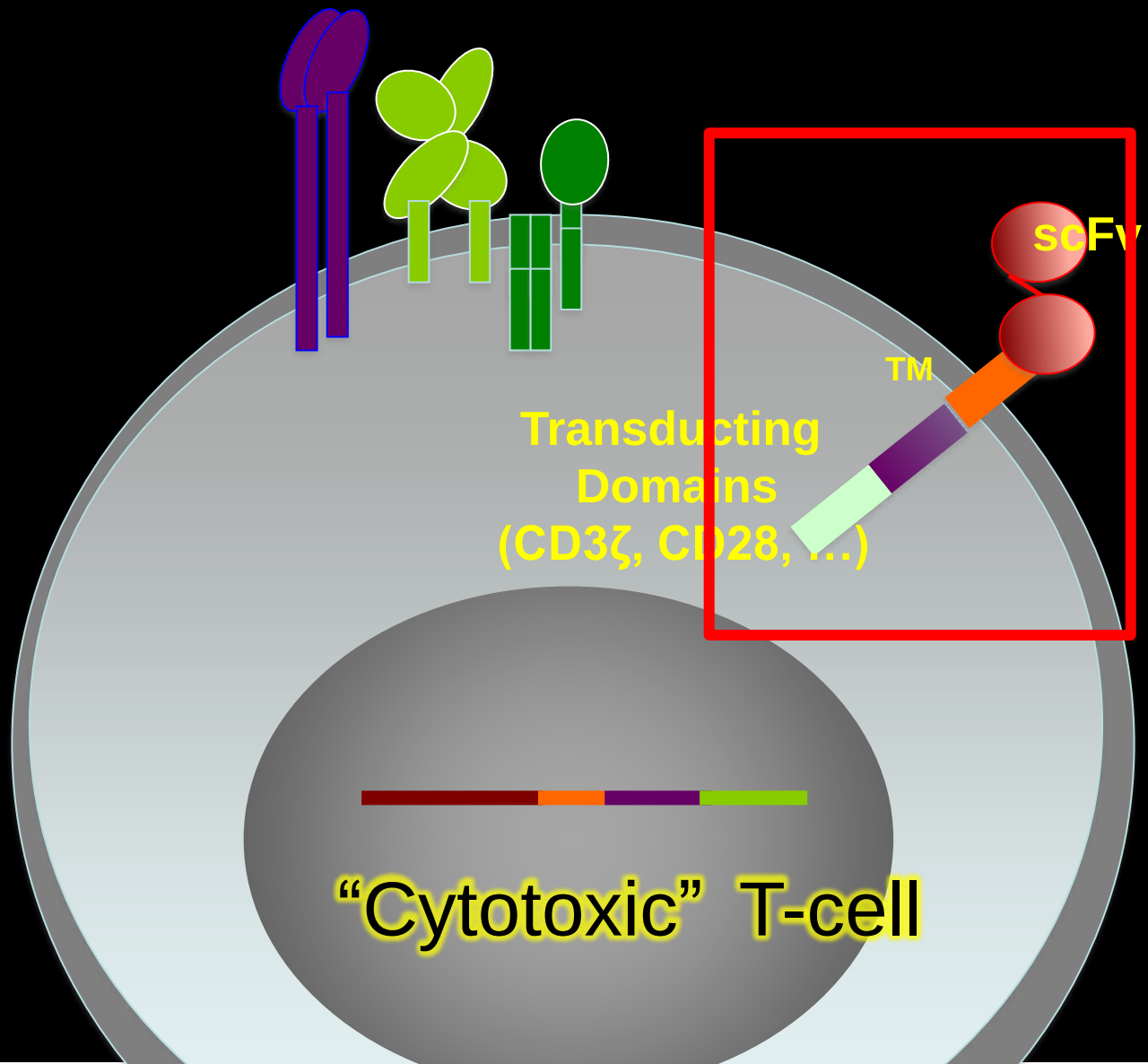
4G
(armored CARs)



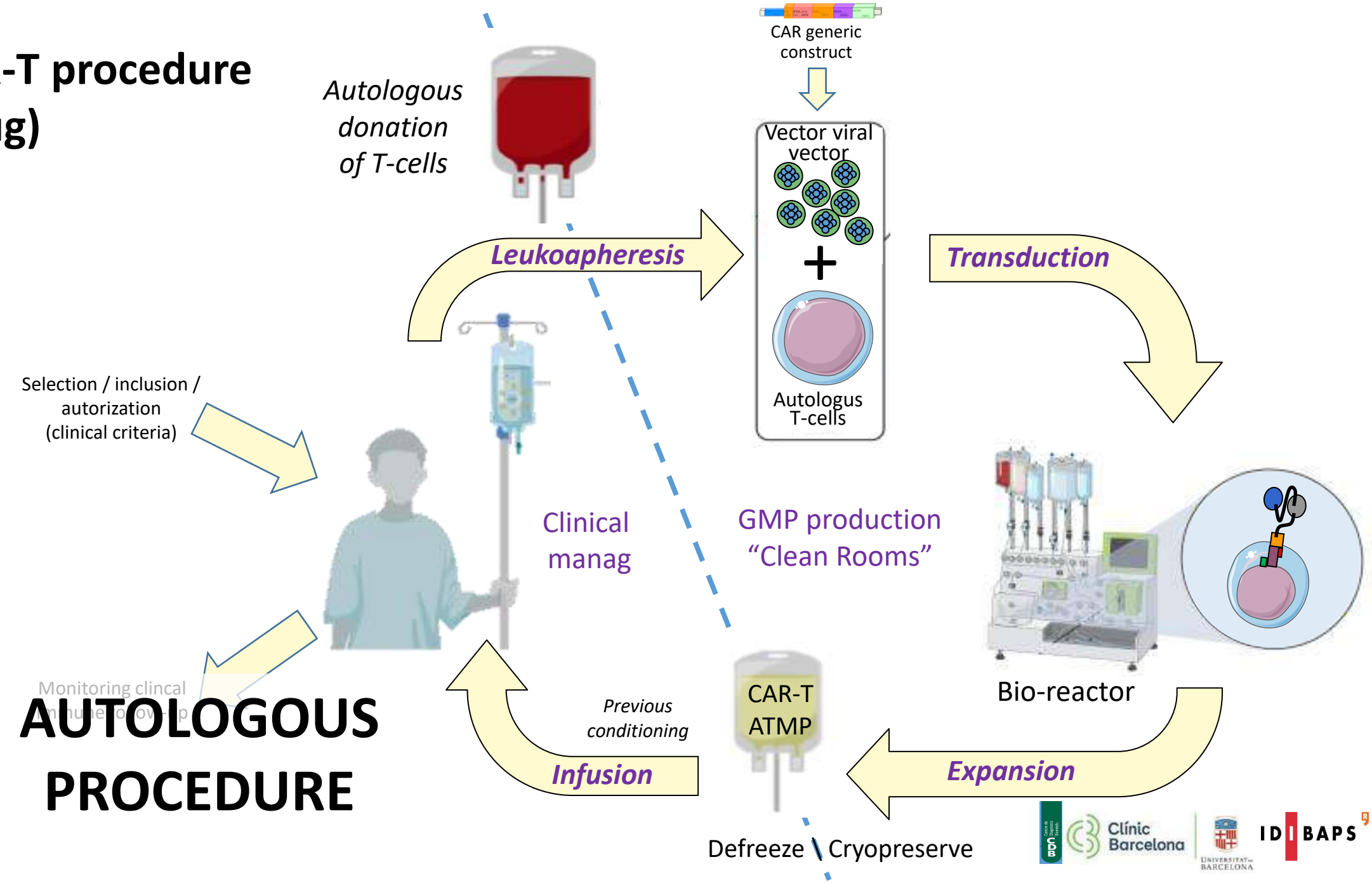
TRUCKs

T cells Redirected for Universal Cytokine Killing

CARs in T-cells = CARTs



CAR-T procedure (drug)



Immunotherapy

Indústria

Good Manufacturig Practice

"Basic" Research

Production

Pharmacology

Clinical Research

Clinical Care

Good Clinical Practice

Infrastructures

Immunotherapy assessment (-) SWOT analysis

Weaknesses ("Immuno"):

- "A lot to know", but "much more to know".
- Lack of "immunologists" and few implicated centers.
- Interrelationship ("Network") and complexity in the molecular interactions of IS.
- Large interpersonal variability.
- "Alternative", "not classical" therapies.
- Lack of immunotherapy monitoring.
- High production costs.

Threats ("context"):

- **"Pharma" regulation.**
- General budget constraints.
- "Interest / s" of Pharma industry.
- "Fears" facing with complexity and "new therapeutic paradigm".

Immunotherapy assessment (+) SWOT analysis

Strengths ("Immuno"):

- "Natural" elements already existing in patients.
- General "high biosecurity".
- Potential for "multi-intervention".
- Intrinsic "personalized medicine"..

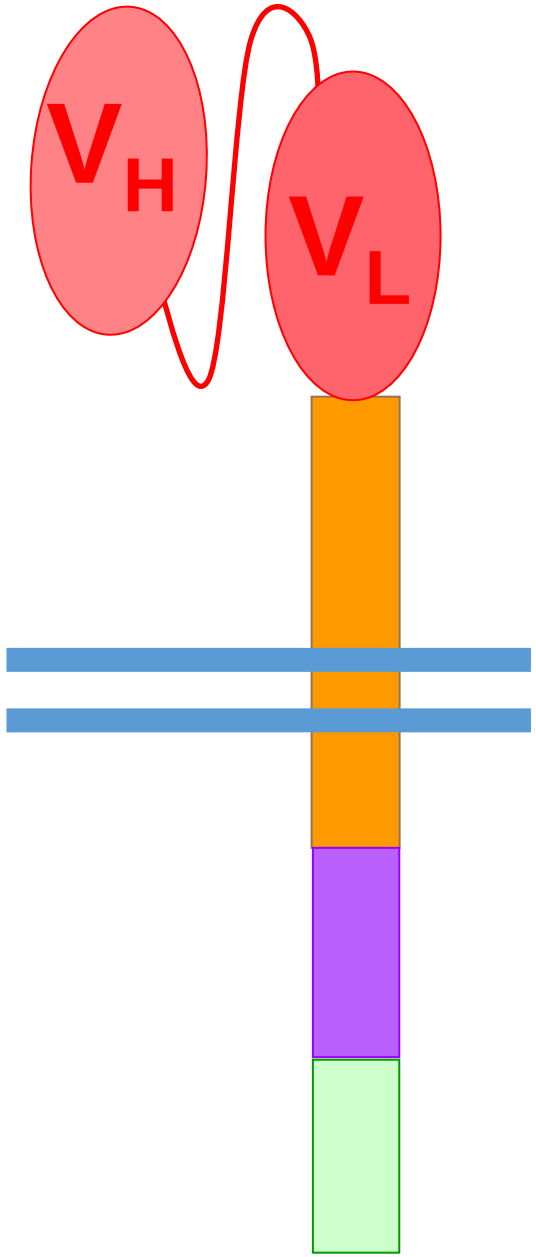
Opportunities ("context"):

- Need to "reorient therapeutic strategy" in front of the economic crisis.
- "General positive perception of people" about IS: it defines health.
- "Relocalization": bring the production points closer to the user.
- **Collaboration between Academy & Biotechs next to conventional Pharma companies.**

Immunotherapy assessment (+) SWOT analysis

Strengths	• "Natural" elements already existing in patients. • General “high biosecurity”. • Potential for “multi-intervention”. • **Intrinsic “personalized medicine”.**	• “A lot to know”, but “much more to know”. • Lack of “immunologists” and few centers. • Interrelationship (“Network”) and compl of IS. • **Large interpersonal variability.** • Lack of immunotherapy monitoring. • **High production costs.**	**Weaknesses**
Opportunities	• “Reorient therapeutic strategy” vs crisis. • “General positive perception of people”. • “Relocalization”: • **Collaboration between Academy & Biotechs next to Pharma.**	• **“Pharma” regulation.** • General budget constraints. • “Interest / s” of Pharma industry. • “**Fears**” facing with complexity and “new therapeutic paradigm	**Threats**

2-G CAR



scFv = Tumor Antigen Recognition

hinge +
Transmembrane
(CD8a … others)

Current CARs

CD137 / CD28 = 2nd signal - 3rd signal

(Costimulatory domain)

CD3ζ = 1st signal

(Signalling domain)

FDA / EMA CART19 / CART-BCMA approved:

Since August-October 2017 (FDA) / July 2018 (EMA) / July 2020 (FDA) / February 2022 (FDA)

KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

NOVARTIS

Novartis ALL & DLBCL <25 y
USA: 475,000 $ / patient)

Spain: 320 m€

NOW APPROVED
YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusio

Kite
A GILEAD Company

Kite NHL DLBCL:
USA 373 m$ / patient

Spain: 320 m€

Breyanzi®
(lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION

Bristol Myers Squibb™

TECARTUS™
(brexucabtagene autoleucel) Susp for IV

Kite MBCL Lymphoma (FDA)

CART-BCMA approved. 2022

Bristol Myers Squibb™
bluebirdbio
Abecma®
(idecabtagene vicleucel) SUSPEN FOR IV IN

CARVYKTI™
(ciltacabtagene autoleucel) Suspension for IV infusion
LEGEND BIOTECH
janssen

Biological principles of CAR T- cells.

CAR-T as antitumoral immunotherapy is based on 3 main factors:

1. The product, engineered T-lymphocytes:
   a) Cytotoxic T-cells (mainly CD8+).
   b) Cytokine producing cells (mainly CD4+).
   c) Capacity of Proliferation (both).
   d) Capacity of cell survival and persistence (both).
2. Own Immune system (the main uncontroled parameter).
3. Clinical management of the process and the patient

KNOW

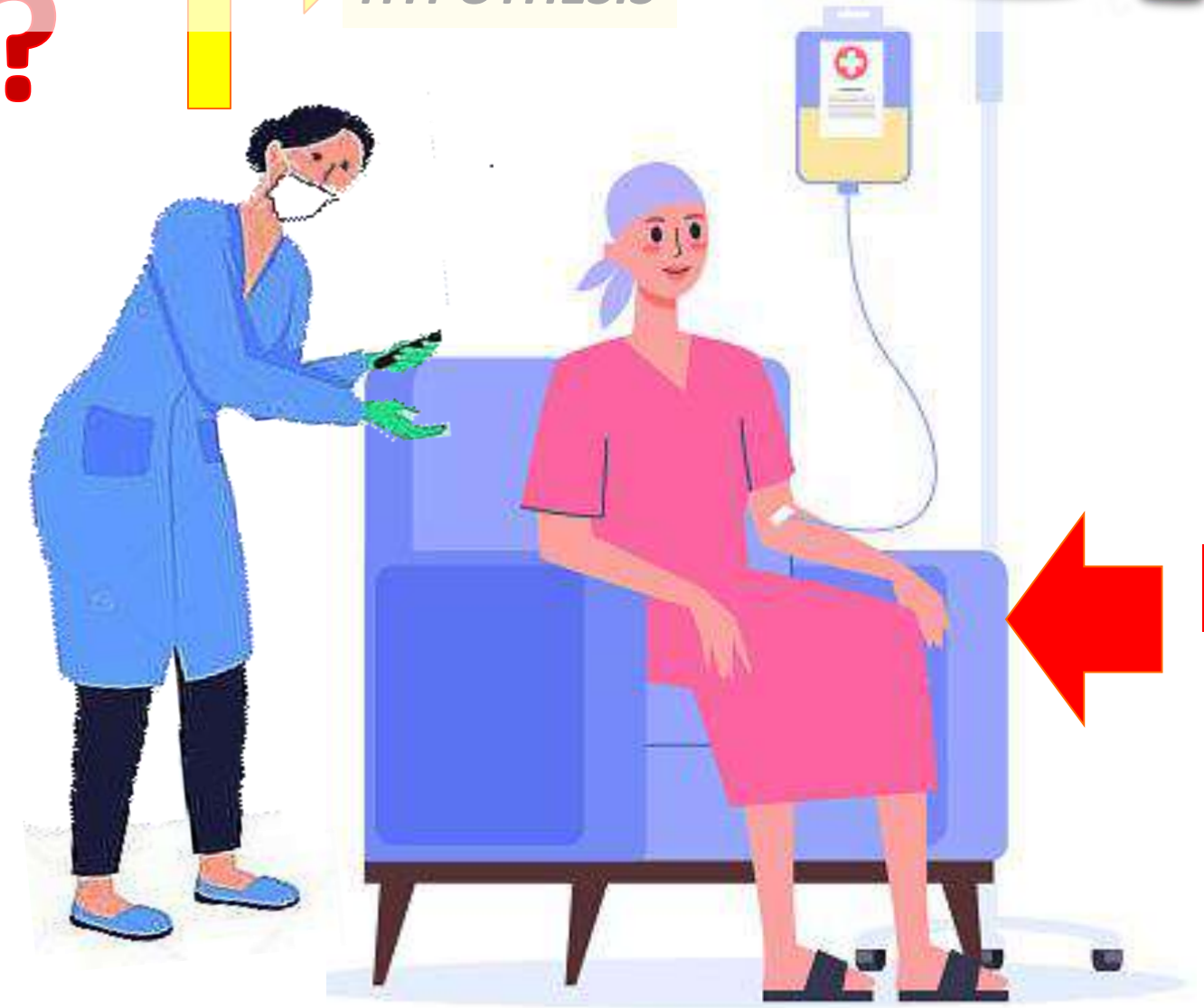
RESULTS

THESIS

Academy

HYPOTHESIS

?



Drug

IMP

Phase ?

CLINICAL TRIALS

UNIVERSITAT DE BARCELONA

IDI

Sant Joan de Déu

45

Academic manufacture of CAR-T.

By now, all the CAR-T have been **initially developed from research teams**, so (by now) **industry is** "just" **defining** how to introduce **large-scale production** (accessibility**?**) and a perfect tracking of the process.

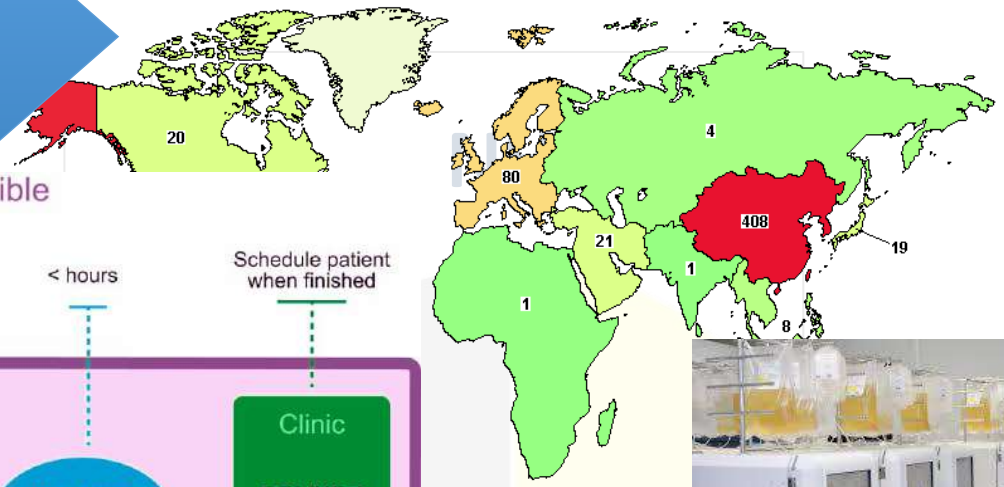
Academic manufacture is (by now) **the base for introducing and improving new proposals**.

But, (by now) **industrial production and marketing** of ATMPs is almost the **only way** to have products.

Success of CARs: Thousands of patients

Commertial development

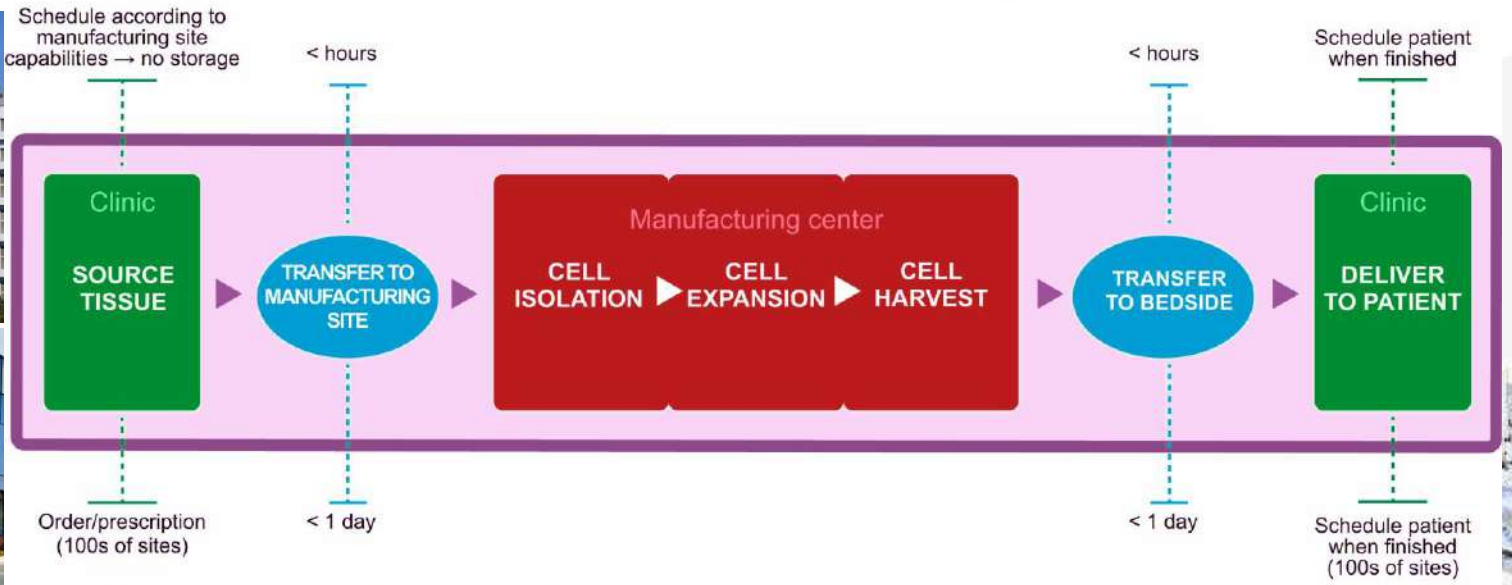
Academic development



Same academic center – close interaction possible

Celgene

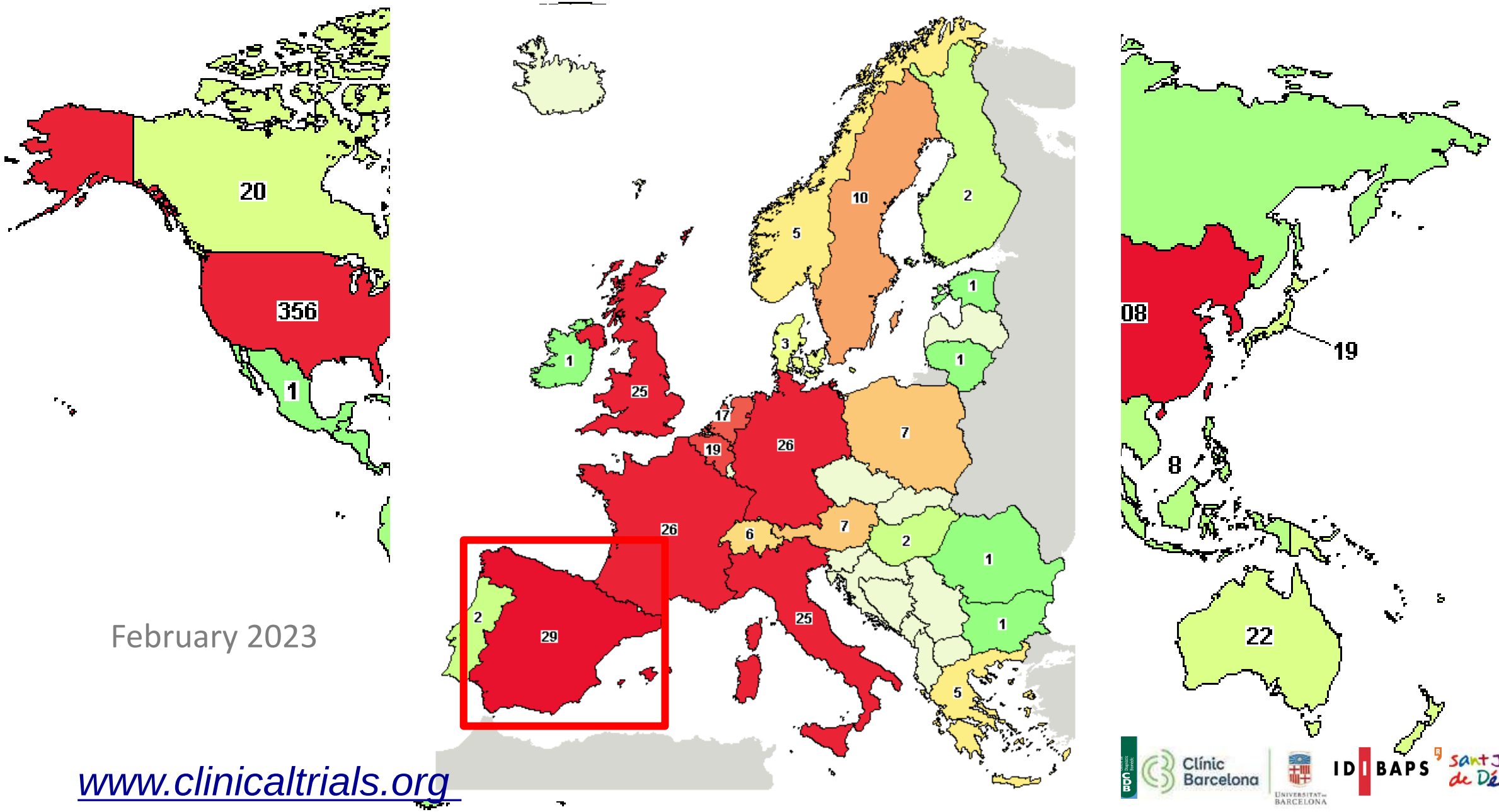
bluebirdbio



Schubert ML/ Schmit

Commercial manufacturing - clinic and manufacturing center are physically disconnected

Clinical Trials “Chimeric Antigen Receptor = 865



February 2023

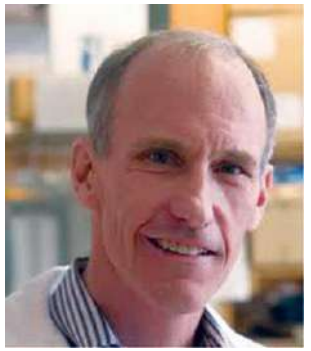
www.clinicaltrials.org

CART19 : August 2011, “seminal” article

The NEW ENGLAND JOURNAL of MEDICINE

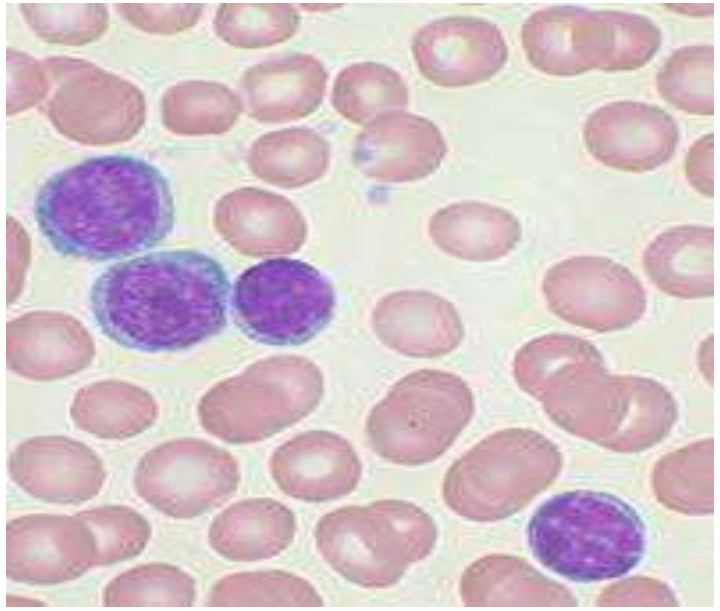
BRIEF REPORT

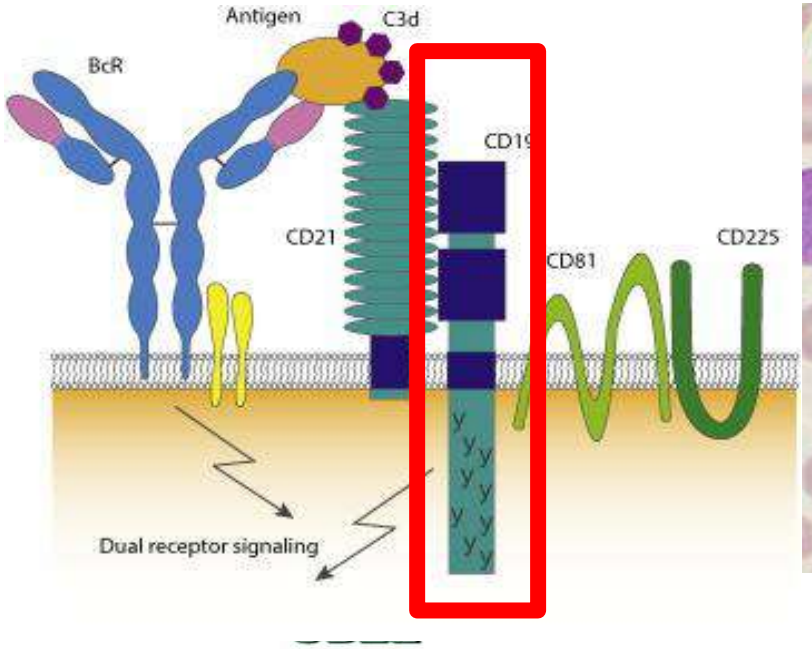
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

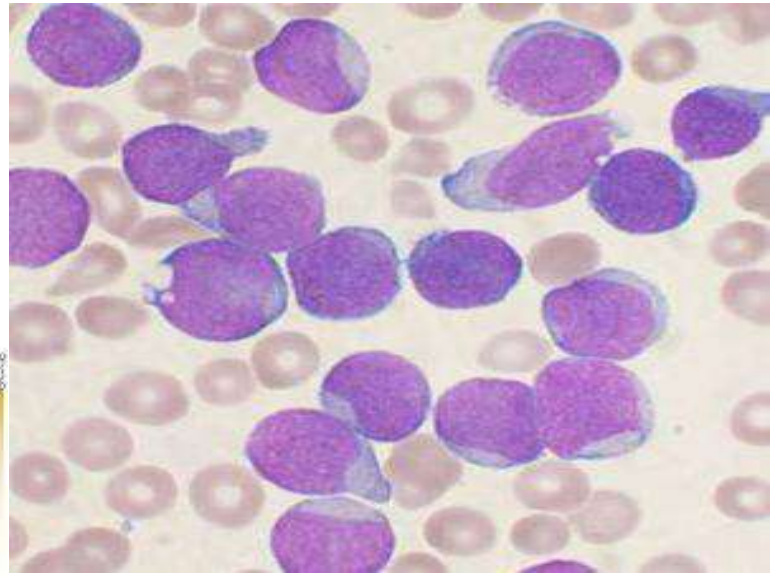


David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

N ENGL J MED 365;8 NEJM.ORG AUGUST 25, 2011

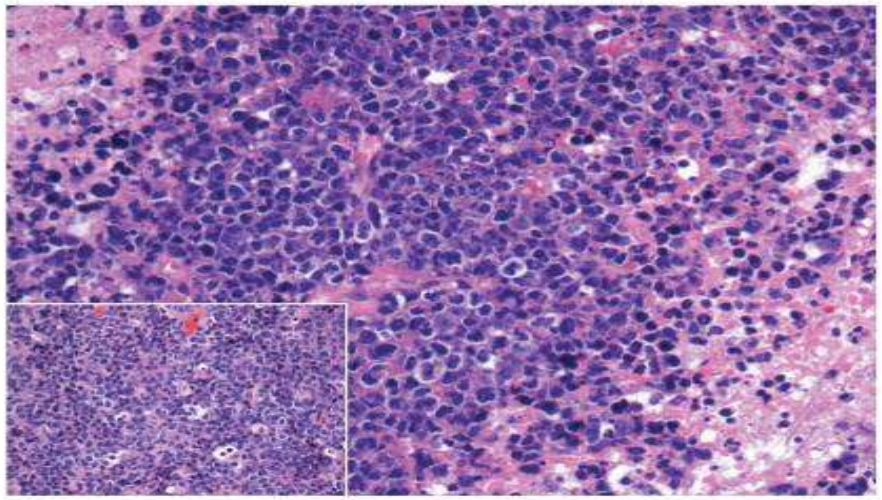






Chronic Lymphocytic Leukemia (CLL)

Acute Lymphoblastic Leukemia (ALL)



Non-Hodgkin Lymphoma (NHL)

The Philadelphia Inquirer

Obituaries

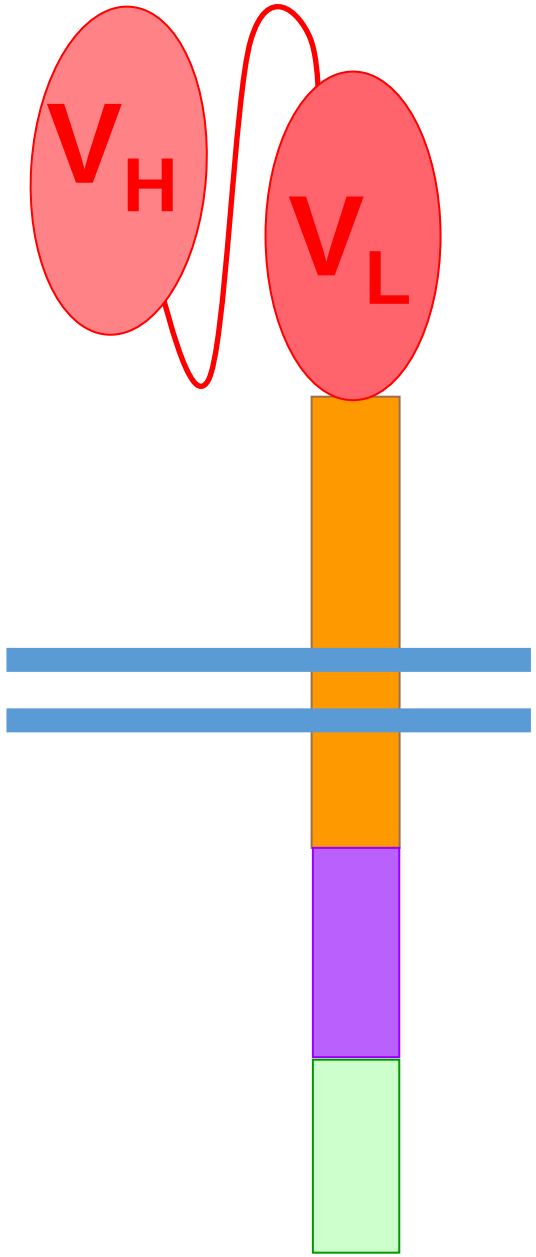
Bill Ludwig, patient who helped pioneer cancer immunotherapy at Penn, dies at 75 of COVID-19

The South Jersey man beat end-stage cancer with a breakthrough immune therapy. But he couldn't beat the pandemic.

Feb 17, 2021


1 Year
3 years
Cancer
7
years
cancer
free!
9
YEAR
10
years
cancer

2-G CAR



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bluebirdbio
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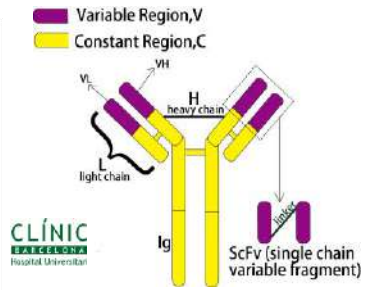
CARVYKTI™
(ciltacabtagene autoleucel) Suspension for IV infusion
LEGEND BIOTECH
janssen

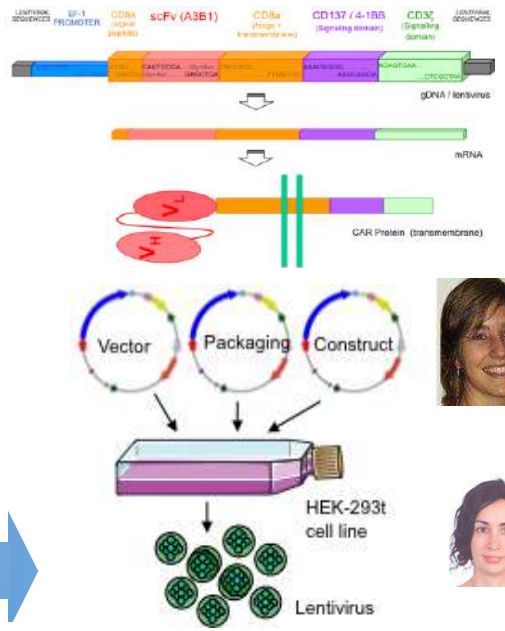
Aim: **Best treatments for our patients!!!**



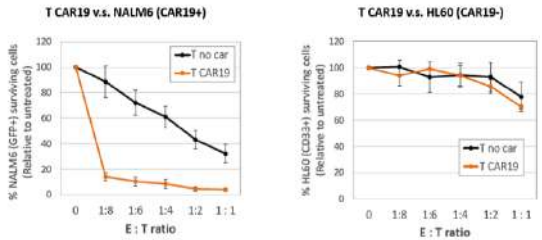
Clone: A3-B1 **(**IgG2a) **1990**
P. Engel, C. Serra, R. Vilella
S Immunologia-CDB - HCP

University of Pennsylvania
Manel Juan – Visiting prof.
Sabbatical by HCP-CDM

CAR design & production



In vitro CAR19-mediated T cell cytotoxic activity

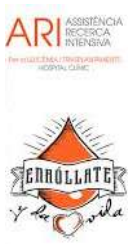


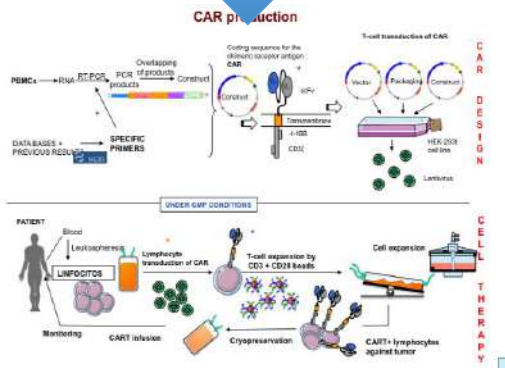
Research projects
PI13/00676
PIE13/00033
PICI14/00122

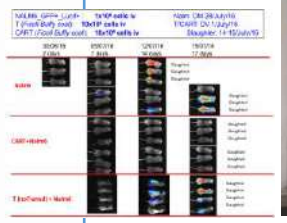
Preclinical steps

PoC proposal

ARI Project



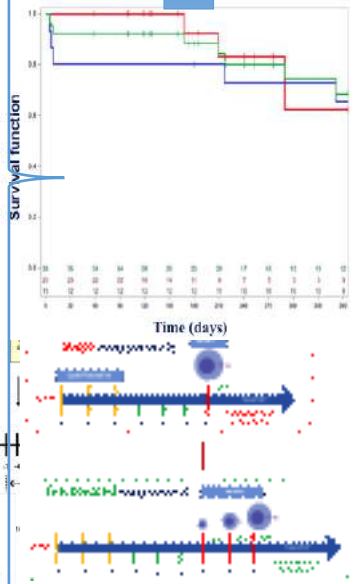




ARI-0001 /CART19-BE-01

Clinical Trial

Hospital Exemption



National & International Partnership

Sant Joan de Déu
BARCELONA

CAR production

CAR DESIGN

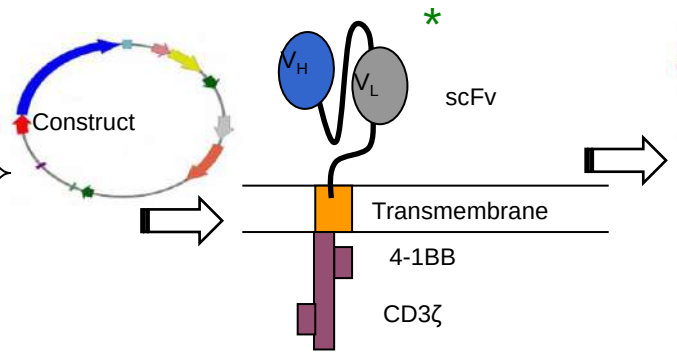
PBMCs → RNA → RT-PCR → PCR products → Overlapping of products → Construct

\+

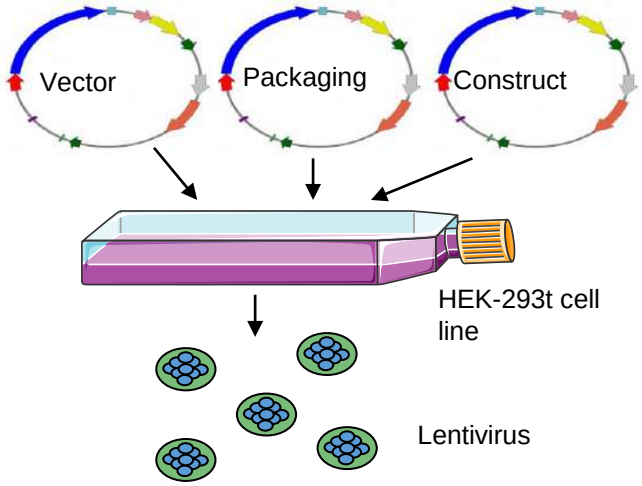
SPECIFIC PRIMERS

DATA BASES + PREVIOUS RESULTS → NCBI

Coding sequence for the chimeric receptor antigen : CAR



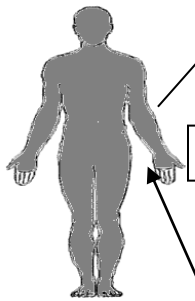
T-cell transduction of CAR



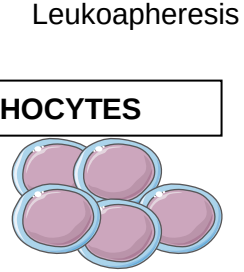
UNDER GMP CONDITIONS

CELL THERAPY

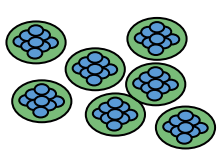
PATIENT

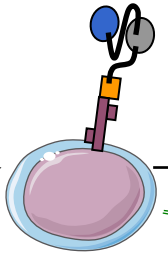


Blood → Leukoapheresis → LYMPHOCYTES

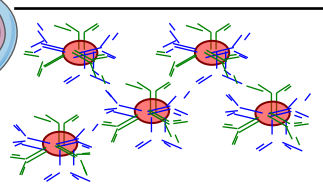


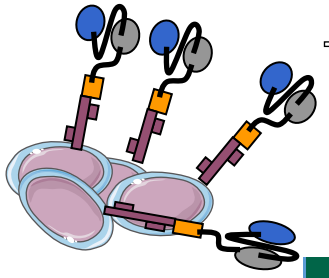
* Lymphocyte transduction of CAR



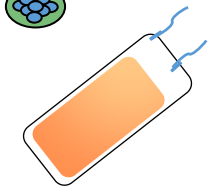


* T-cell expansion by CD3 + CD28 beads



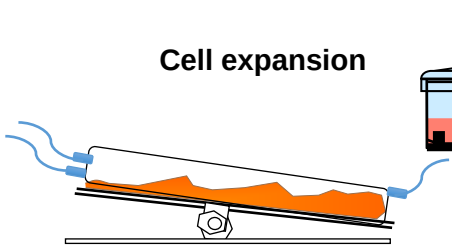


Cryopreservation



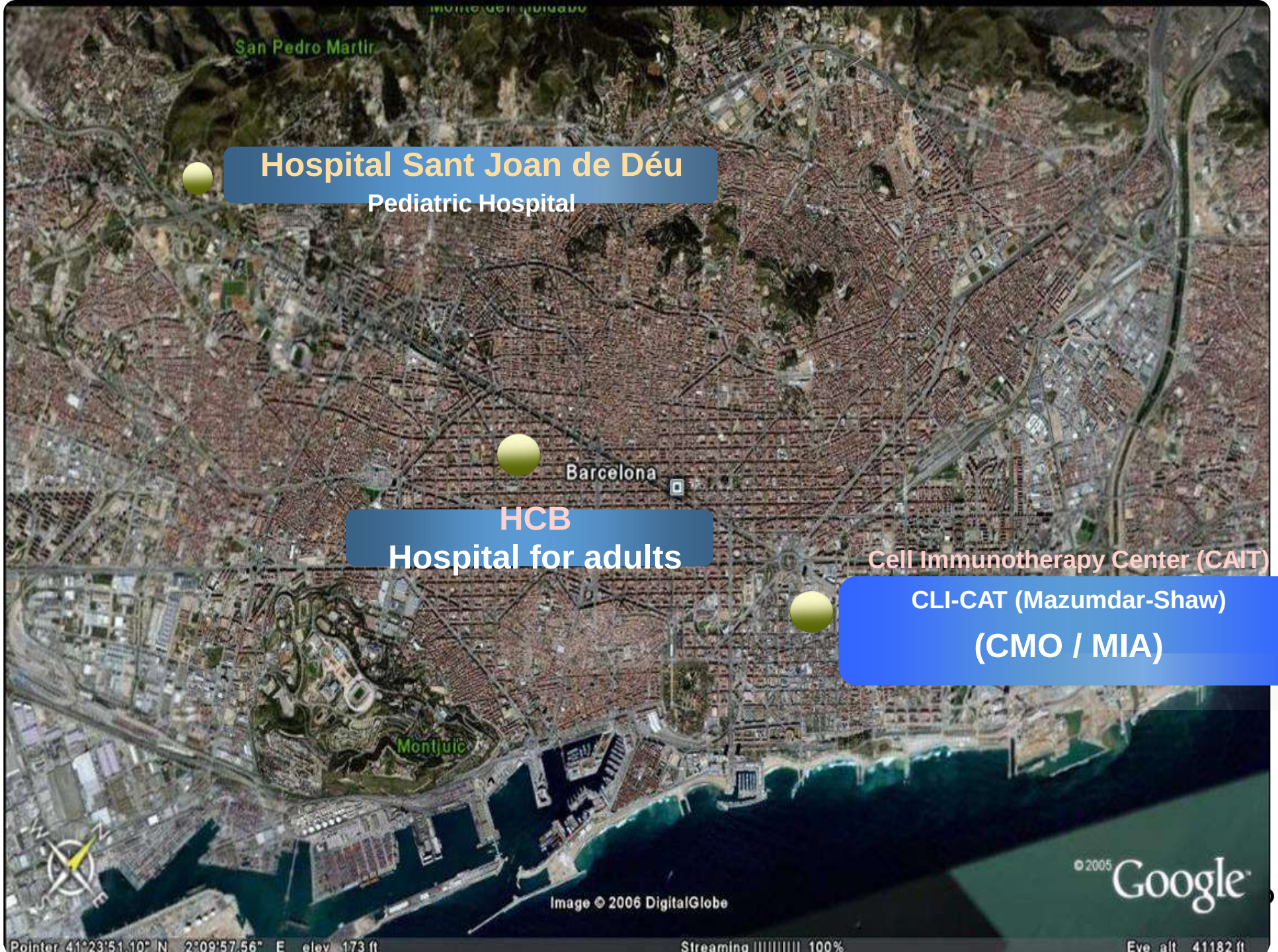
CART infusion

Monitoring

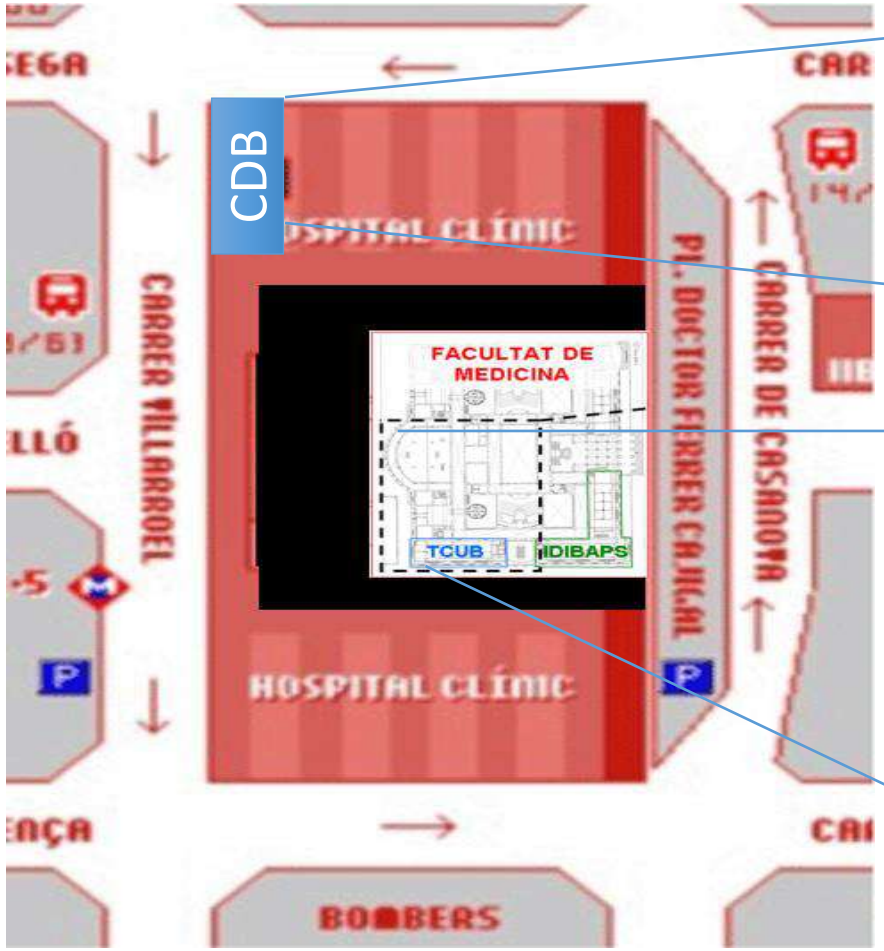


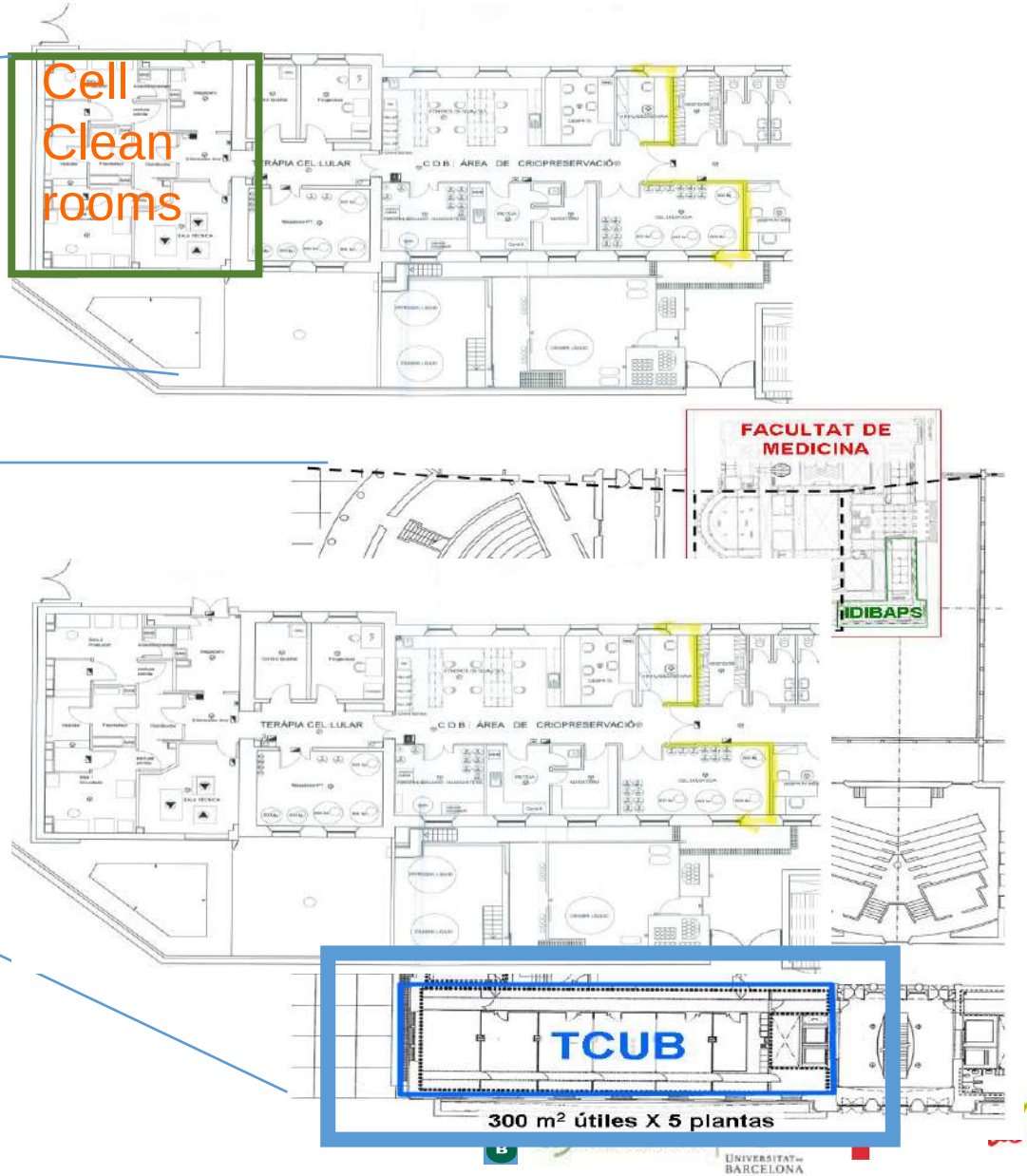
Cell expansion

CART+ lymphocytes against tumor

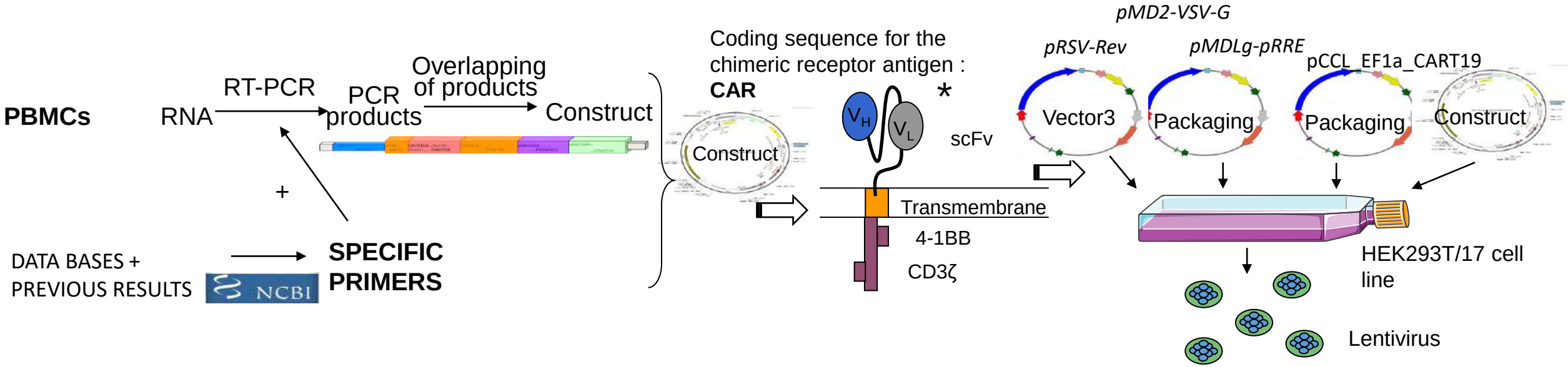

San Pedro Martir
Hospital Sant Joan de Déu
Pediatric Hospital
Barcelona
HCB
Hospital for adults
Cell Immunotherapy Center (CAIT)
CLI-CAT (Mazumdar-Shaw)
(CMO / MIA)
Montjuic
Image © 2006 DigitalGlobe
© 2005 Google
Pointer 41°23'51.10" N 2°09'57.56" E elev 173 ft
Streaming 100%
Eye alt 41182 ft

GMP facilities at HCB - UB



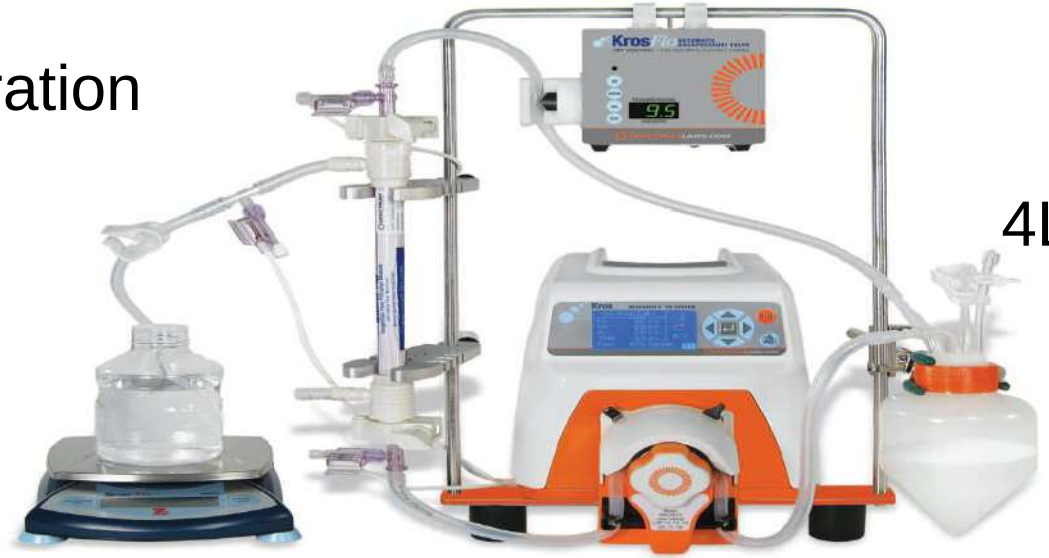


Production of Lentiviral Vector



Ultrafiltration

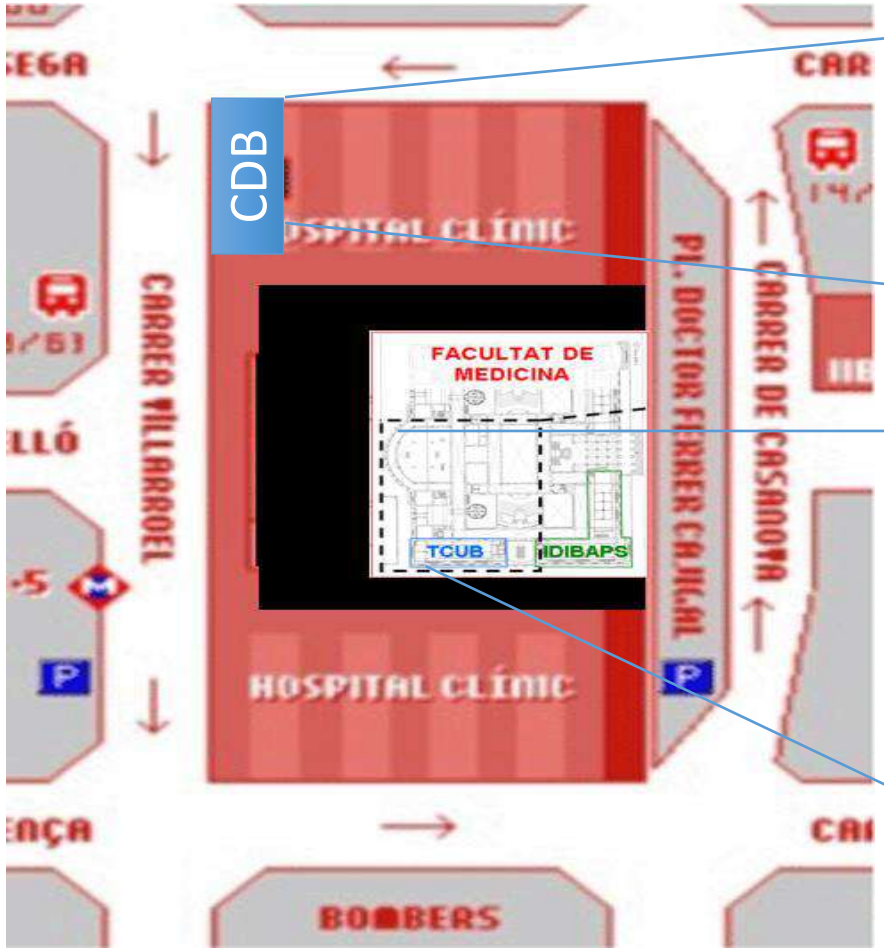
100mL

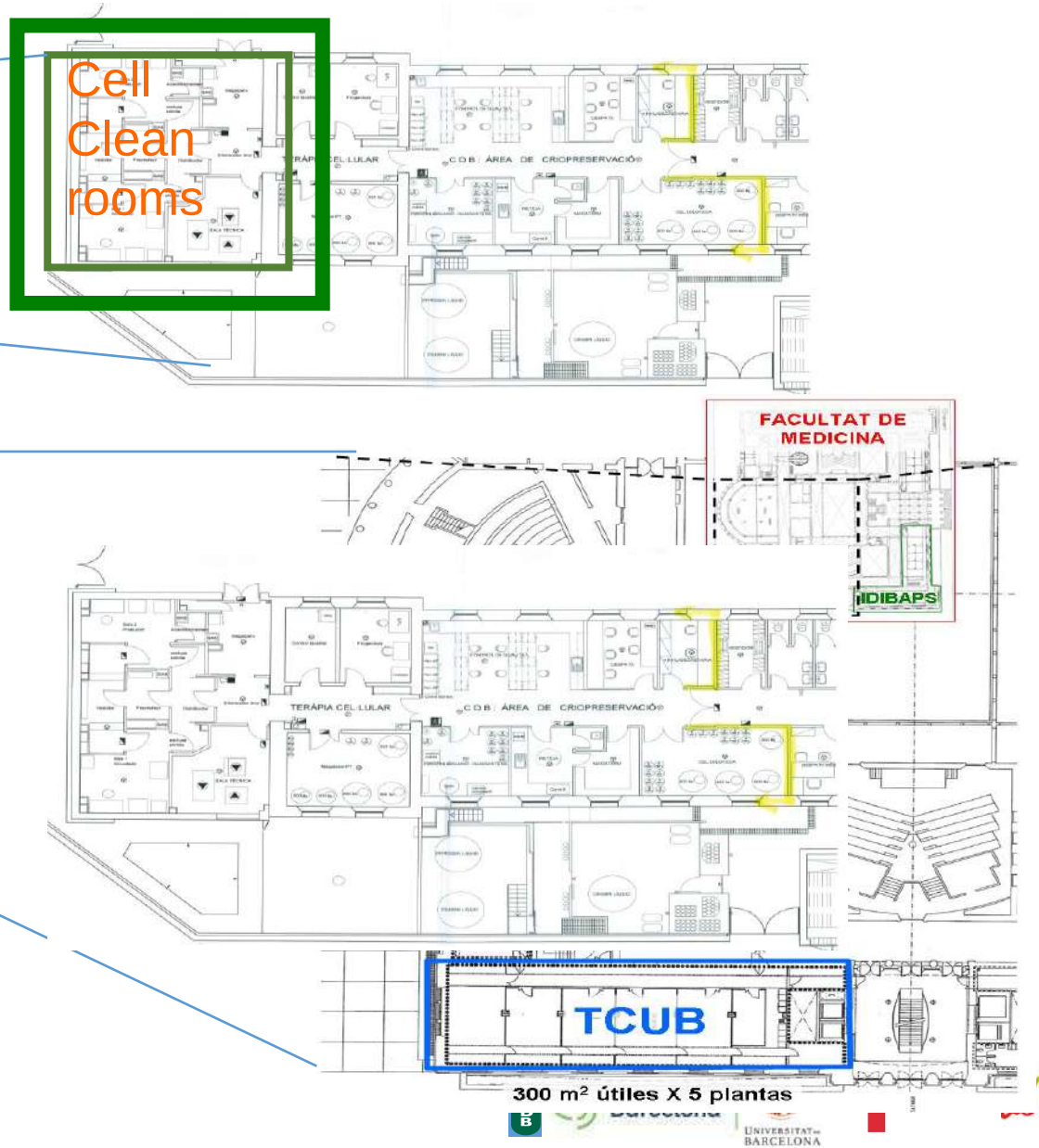


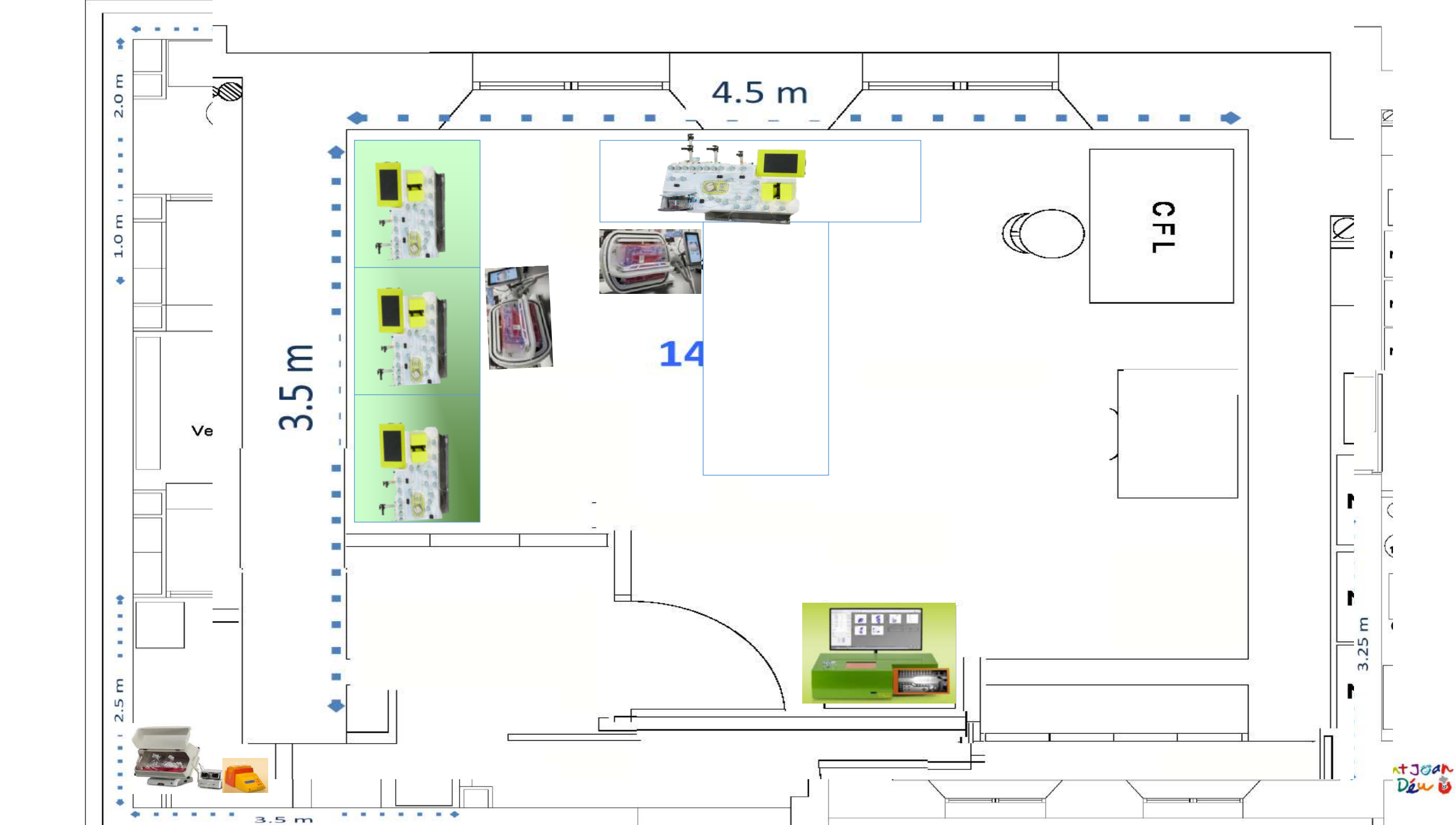
4L

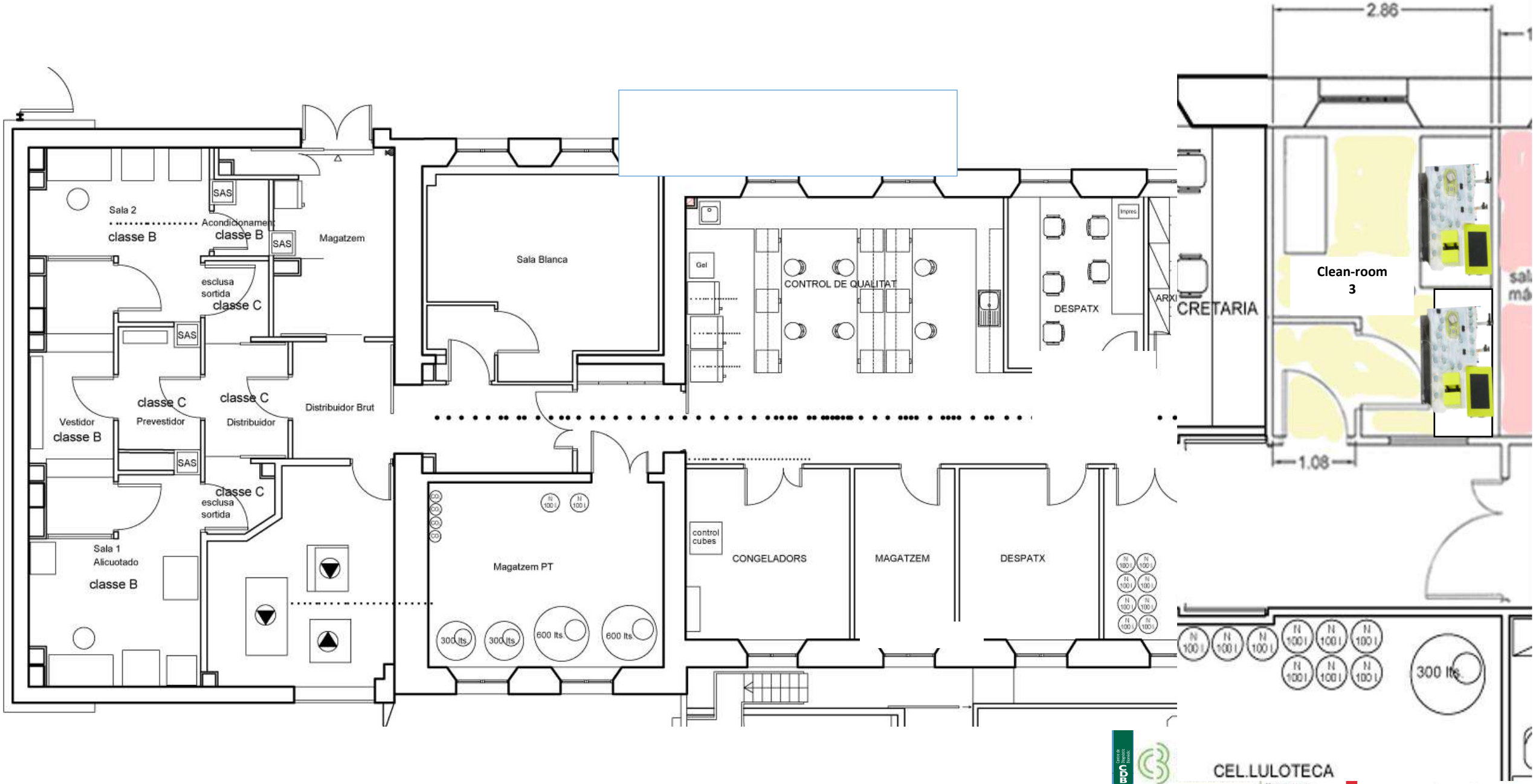
Recollection

GMP facilities at HCB - UB



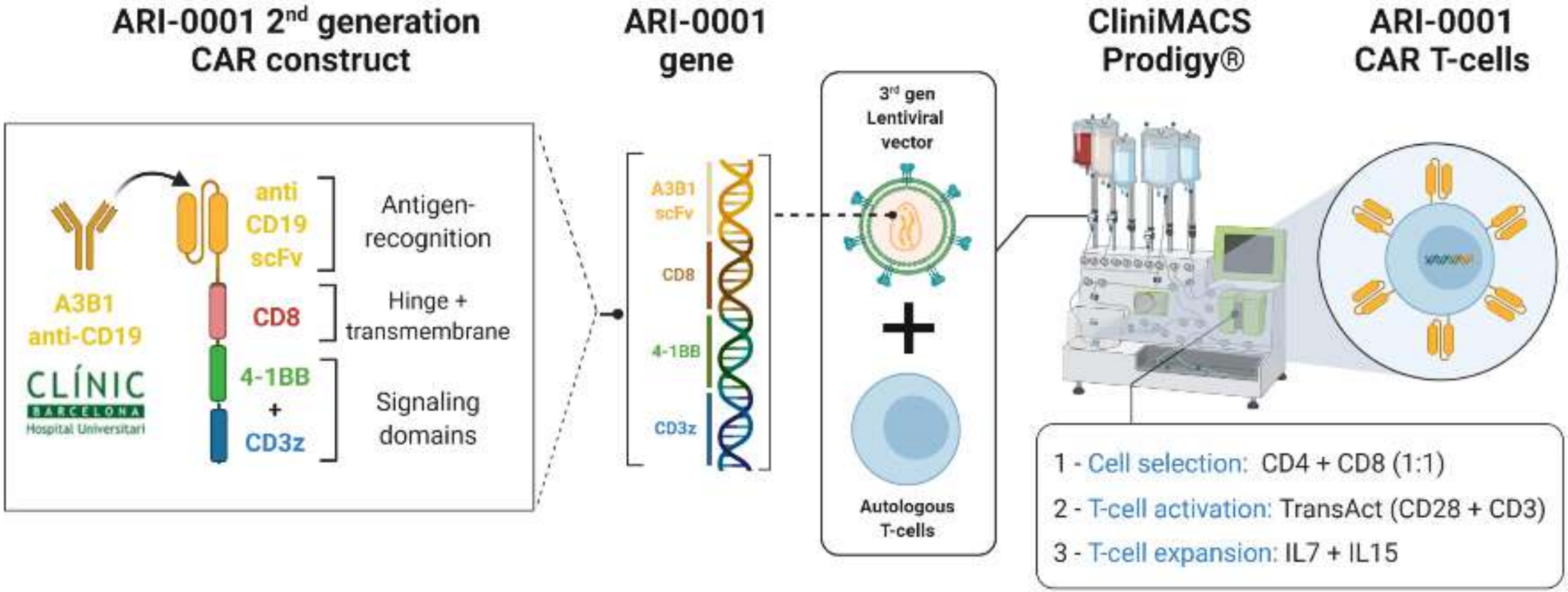



4.5 m
2.0 m
1.0 m
3.5 m
Ve
14
CFL
2.5 m
3.5 m
3.25 m

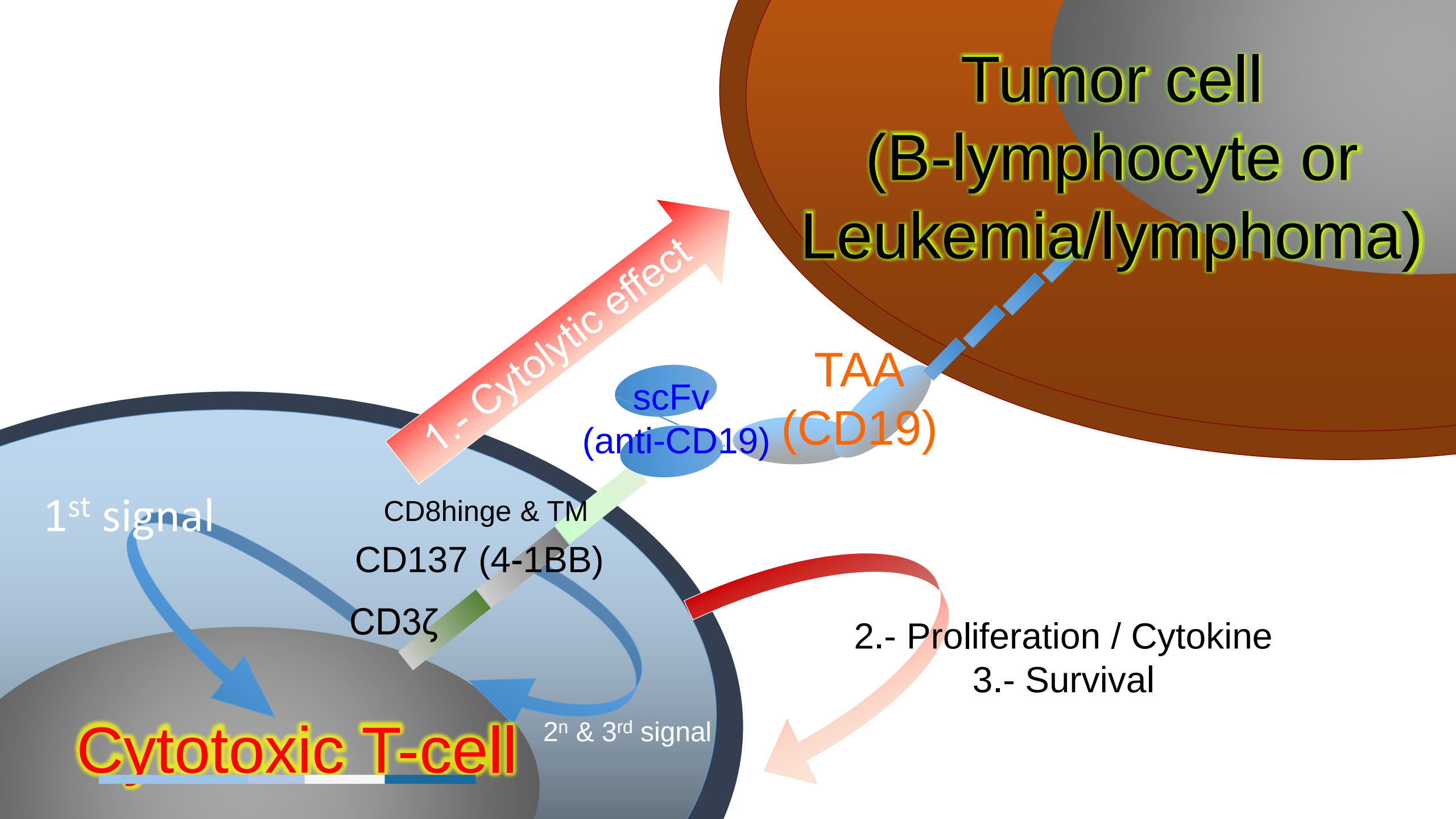

Sala 2
classe B
Acondicionament
classe B
SAS
SAS
Magatzem
esclusa
sortida
classe C
SAS
classe C
classe C
Distribuidor Brut
Vestidor
classe B
Prevestidor
Distribuidor
SAS
classe C
esclusa
sortida
Sala 1
Alicuotado
classe B
Sala Blanca
Gel
CONTROL DE QUALITAT
DESPATX
Impres
ARXI
CRETARIA
Clean-room
3
2.86
1.08
Magatzem PT
300 lts
300 lts
600 lts
600 lts
control
cubes
CONGELADORS
MAGATZEM
DESPATX
300 lts
CEL.LULOTECA
UNIVERSITAT DE BARCELONA


Fundació Glòria Soler

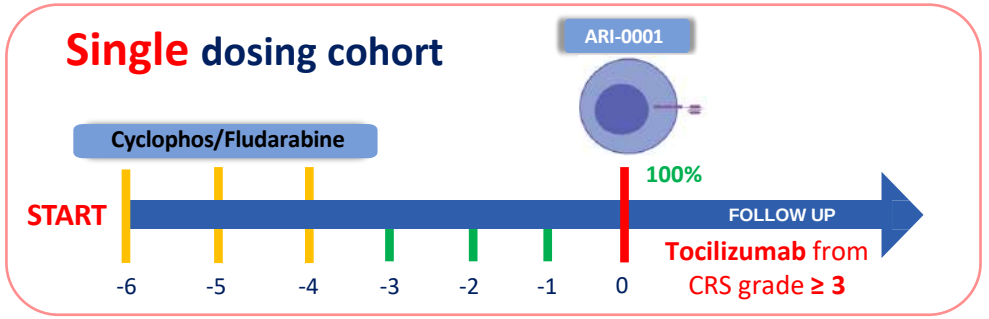
ARI-0001 cells *(varnimcabtagene autoleucel [varim-cel])*

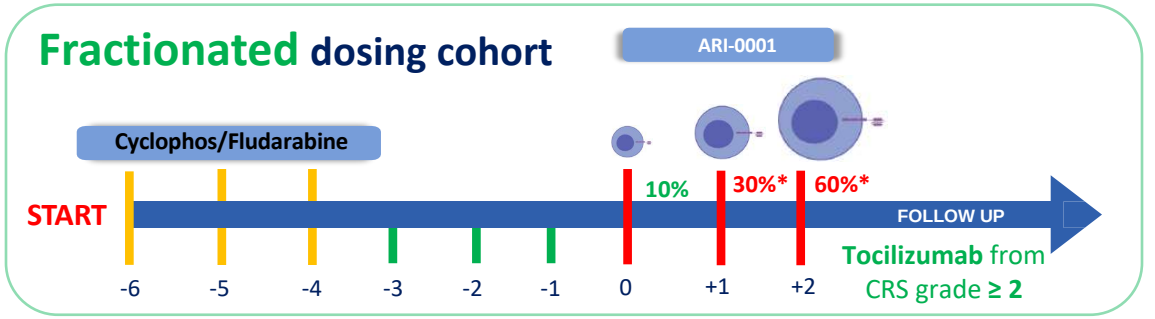


Castella M, et al. *Mol. Ther.* 2019


Tumor cell
(B-lymphocyte or
Leukemia/lymphoma)
1.- Cytolytic effect
TAA
(CD19)
scFv
(anti-CD19)
CD8hinge & TM
CD137 (4-1BB)
CD3ζ
1st signal
2n & 3rd signal
2.- Proliferation / Cytokine
3.- Survival
Cytotoxic T-cell

Safety & dose administration





N:	19 patients (15 B-ALL, 3 NHL, 1 CLL)	18 patients (16 B-ALL, 2 NHL)
Median dose:	1 x 10^6 CART19+ / kg (0.5 - 5)	1 x 10^6 CART19+ / kg (0.4 – 2)* *Dosing was limited at 40% in 3/18 (17%) patients due to CRS onset, the rest (83%) received full dose
Neurotox:	**16%**	**17%**
CRS:	▪ **Grade 1-5** in 16/19 (**84%**) of patients ▪ **Grade ≥ 3** in 5/19 (**26%**), all requiring tocilizumab	▪ **Grade 1-5** in 8/18 (**44%**) of patients ▪ **Grade ≥ 3** in 0/18 (**0%**), with 1 pt. receiving tocilizumab
Procedure related deaths:	**16%** ○ Grade 5 CRS (2 ALL pts.) ○ Pseudomembranous colitis (*C. difficile*) + grade 3 CRS (1 ALL pt.)	**0%**

CART19-BE-01: Efficacy (ALL)

Patients	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	OS, median (CI 95%)	Reference
38 (11 kids + 27 adults)	71% (54-85%)	12.0 mo (4.2-20.2) 47% (27-67%) at 1y	20.2 m (10.4-ND) 69% (49-88%) at 1y	CART19-BE-01
PEDIATRICS				
11 kids (up to 18y)	55% (23-83%)	18.1 mo (14.5-ND) 82% (59-100%) at 1y	NA (7.1-NA) 78% (50-100%) at 1y	CART19-BE-01
75 kids (up to 25y)	81% (71-89%)	50% (35-64%) at 1y	76% (63-86%) at 1y	Maude et al
21 kids (up to 30y)	67% (43-85%)	79% at 5 mo	51.6% at 10 mo	Lee et al
45 kids (up to 25y)	93%	51% (37-70%) a 1y	69.5% (56-87%) at 1y	Gardner et al
ADULTS				
27 adults (> 18y)	78% (58%-91%)	9.4 mo (3.3-20.2) 34% (12-57%) at 1y	20.2 mo (12.8-NE) 65% (40-89%) at 1y	CART19-BE-01
53 adults	83% (70-92%)	6.1 mo (5.0-11.5)	12.9 mo (8.7-23.4)	Park et al
35 adults	69% (51-83%)	5.6 mo	19.1 mo (6.2-NE)	Frey et al
53 adults	85%	7.6 mo	20.0 mo	Hay et al
55 adults	71% (57-82%)	11.6 mo (2.7-15.5)	18.2 mo (15.9-NE)	Shah et al

Ortiz-Maldonado et al. Mol Ther 2021

Current ARI-0001 General Overview

Treated Patients:

- **CART19-BE-01 trial: 47 patients**
  (a bi-center trial for ALL, NHL and CLL)
- **The compassionate use program: 82 patients**
  (a bi-center program for ALL, NHL and CLL without curative options)
- **The hospital exemption program: 13 patients**
  (a program for R/R ALL >25 years)
- **CART19-BE-02 trial: 20 patients (12 pending)**
  (a multicenter [9] trial for R/R adult ALL)
- **CART19-BE-03 trial: 30 paedriatic patients (for presentation to AEMPS)**
  (a multicenter [5] trial for R/R pediatric ALL)
- **CART19BCMA-BE-001: LNH**
  (a multicenter [5] trial for B-NHL)
- **International collaborations**
  (HOVON, Immuneel, Cellpoint, specific for different countries (11 petitions around de world)

ARI-0001 Hospital Exemption (HE) authorization:

- First ATMP to be authorized through HE for cancer in Europe
- First European CAR-T product to be authorized for adult B-ALL (≥ 25yr)
- First ‘public’ CAR-T product to be authorized

Clinical grade outcomes with ARI-0001

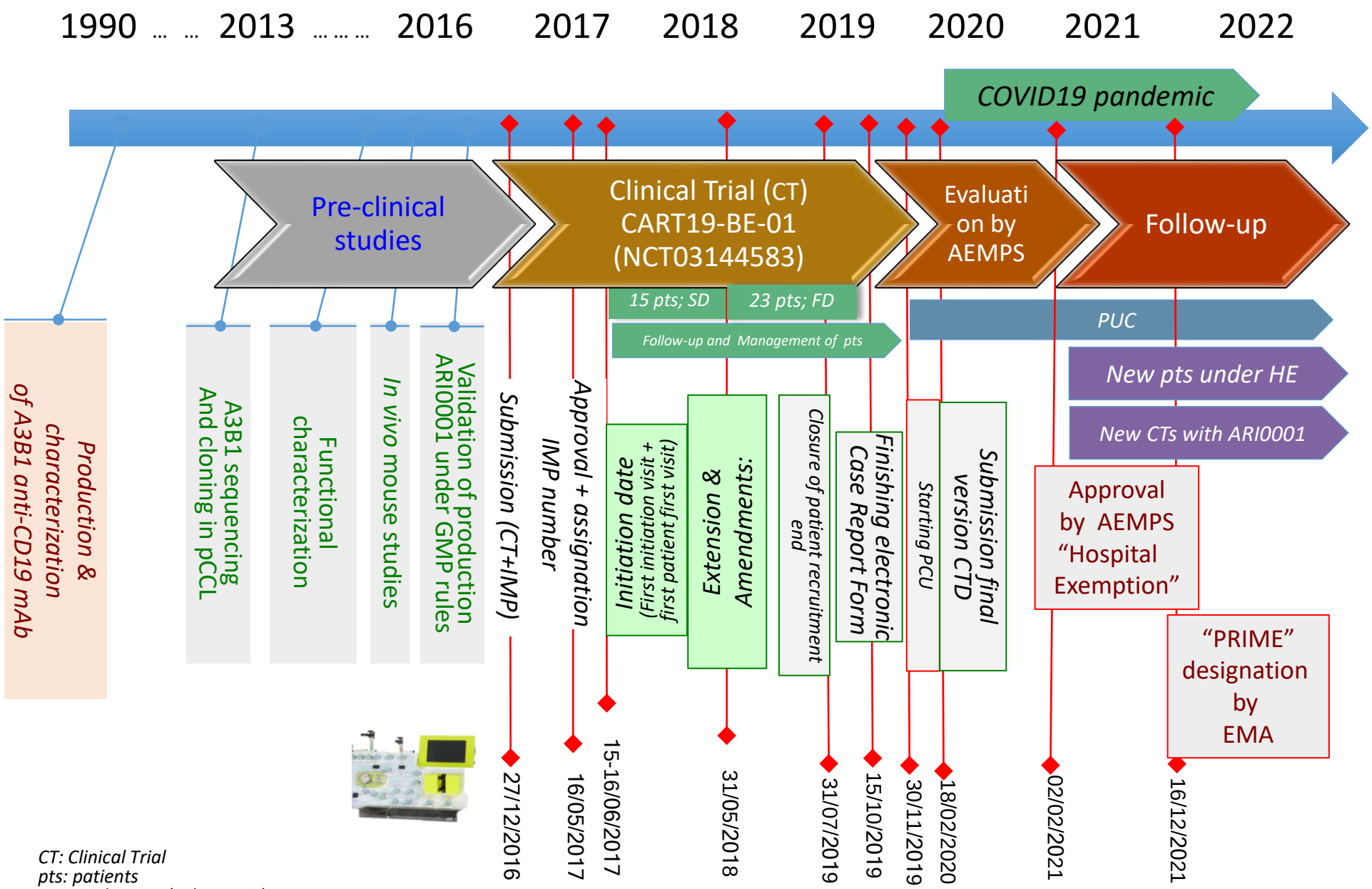
Published results:

- **Point-of-care ARI-0001 cell production** (DOI: 10.3389/fimmu.2020.00482)
- **Early outcomes of the CART19-BE-01 trial** (DOI: 10.1016/j.ymthe.2020.09.027)
- **Long term follow-up of ARI-0001 for R/R B-ALL** (DOI: 10.1136/jitc-2021-003644)
- **ARI-0001 cells for isolated extramedullary disease ALL** (DOI: 10.1002/ajh.26519)
- **ARI-0001 cells for CLL and Richter's** (DOI: 10.3389/fonc.2022.828471)

RESUELVE

Conceder la autorización de uso del medicamento de terapia avanzada de fabricación no industrial **"ARI-0001 dispersión para perfusión, que contiene 0,1-1x10^6 células/kg – Hospital Clínic de Barcelona ", en el ámbito y con las condiciones que se especifican a continuación:**

Código Nacional:	Formato:
730228	**ARI-0001 dispersión para perfusión, que contiene 0,1-1x10^6 células/kg – Hospital Clínic de Barcelona, 1 bolsa de criopreservación CryoMacs de 30 ml**

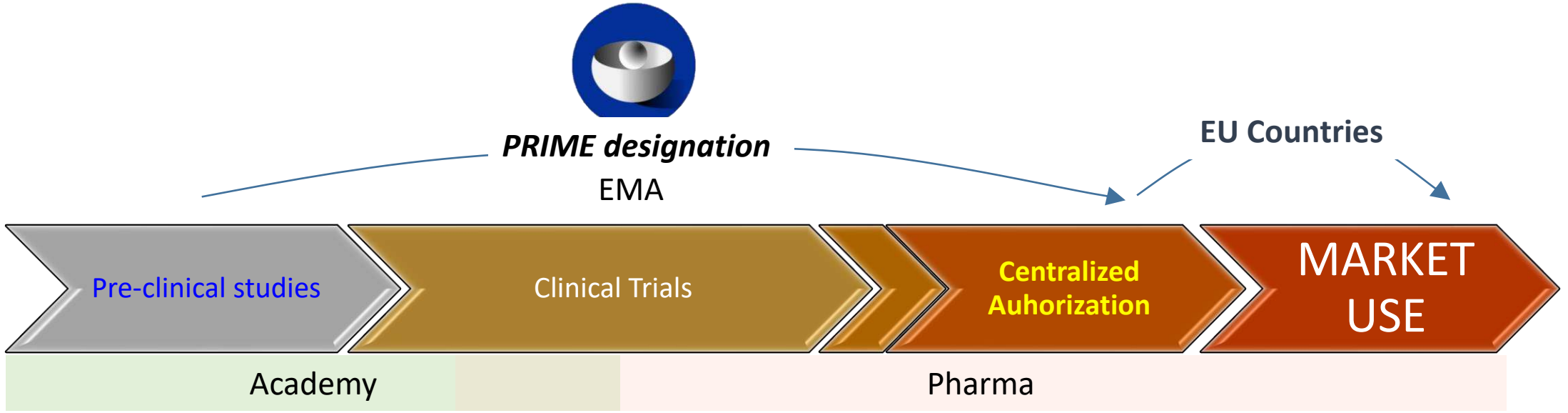


CT: Clinical Trial
pts: patients
SD: Single Dose (cohort 1+2)
FD: Fractionated dose (cohort 3)
CTD: Common Technical Document of the CT
PCU: Program of Compassionate Use

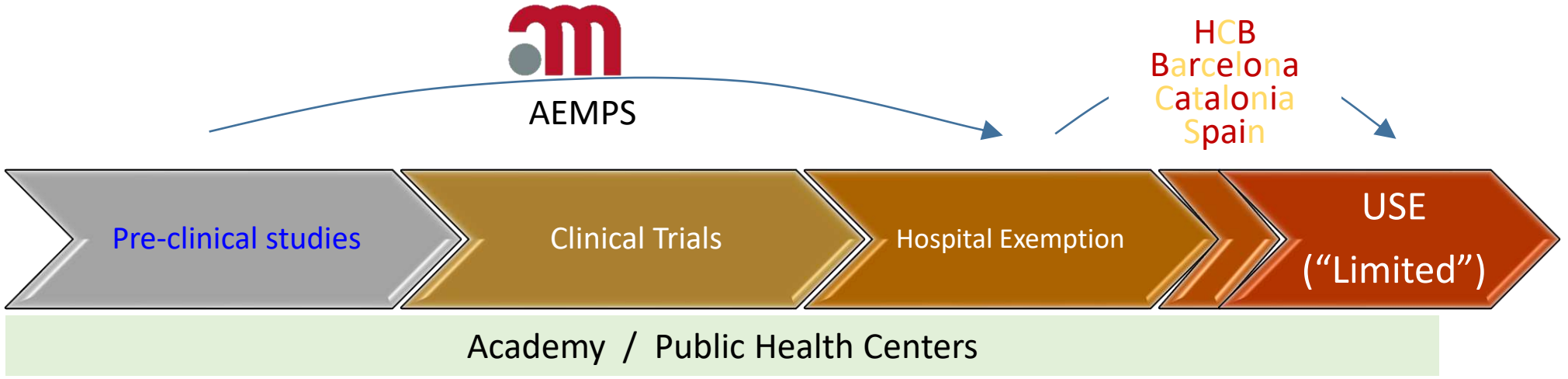
Treating with CAR T-cells (not only academic ATMPs)

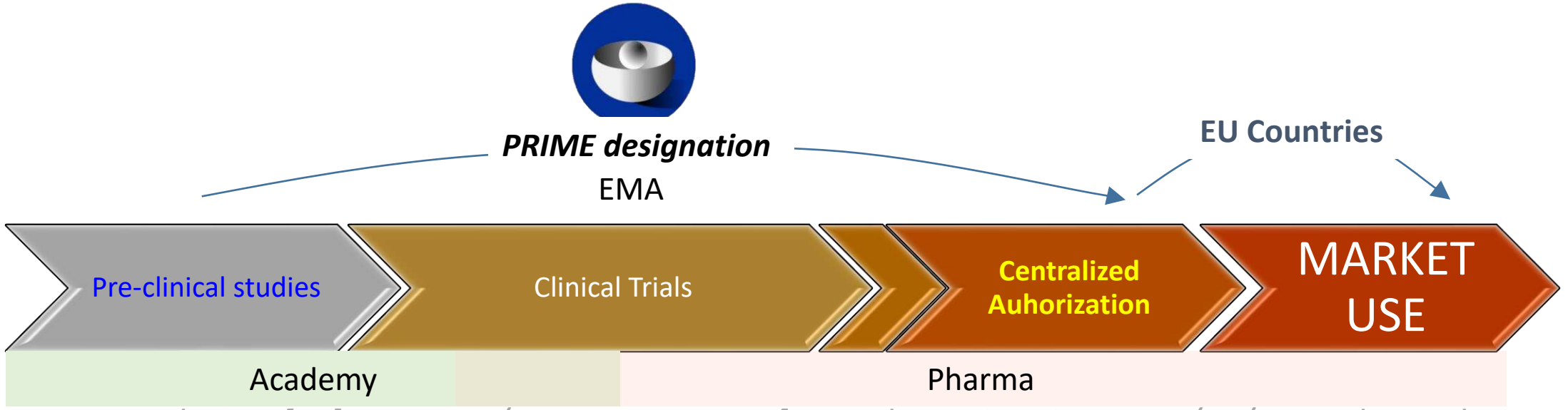
Starting considerations:

- Clinical trials are the first “obvious tool” (cost?) -> a pathway to approval (reimbursement?)
- Aims of the regulatory systems:
  - To assure **safety** and **quality** of **products** (ATMPs???)
  - To ensure **access** of products to **patients** (in the countries) !!!
  - *To help in the arrival of new products, especially when there are unmet medical needs? (or proposals for improvement?)*
  - *To collaborate with public health systems ? (public / non profit developers = private / profit industry?)*
- Open questions:
  - Who should define the regulatory rules? (own regulators, industry, patients, …)
  - When and how the regulatory rules should be adapted/changed?
  - Autologous ATMPs should be equally regulated as Allogenic or products?



European Regulation [EC] No 1394/2007 on ATMPs [amending Directive 2001/83/EC and Regulation No 726/ 2004] establish the legal framework for ATMPs -> "HE" (developed differentially in each EU country).





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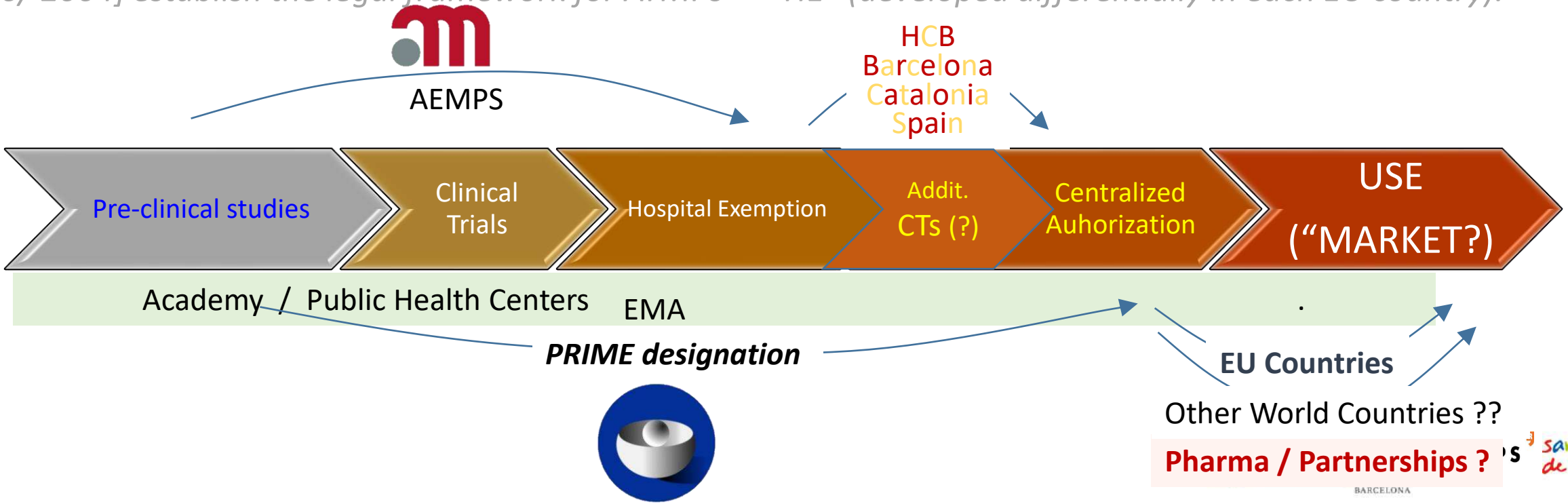
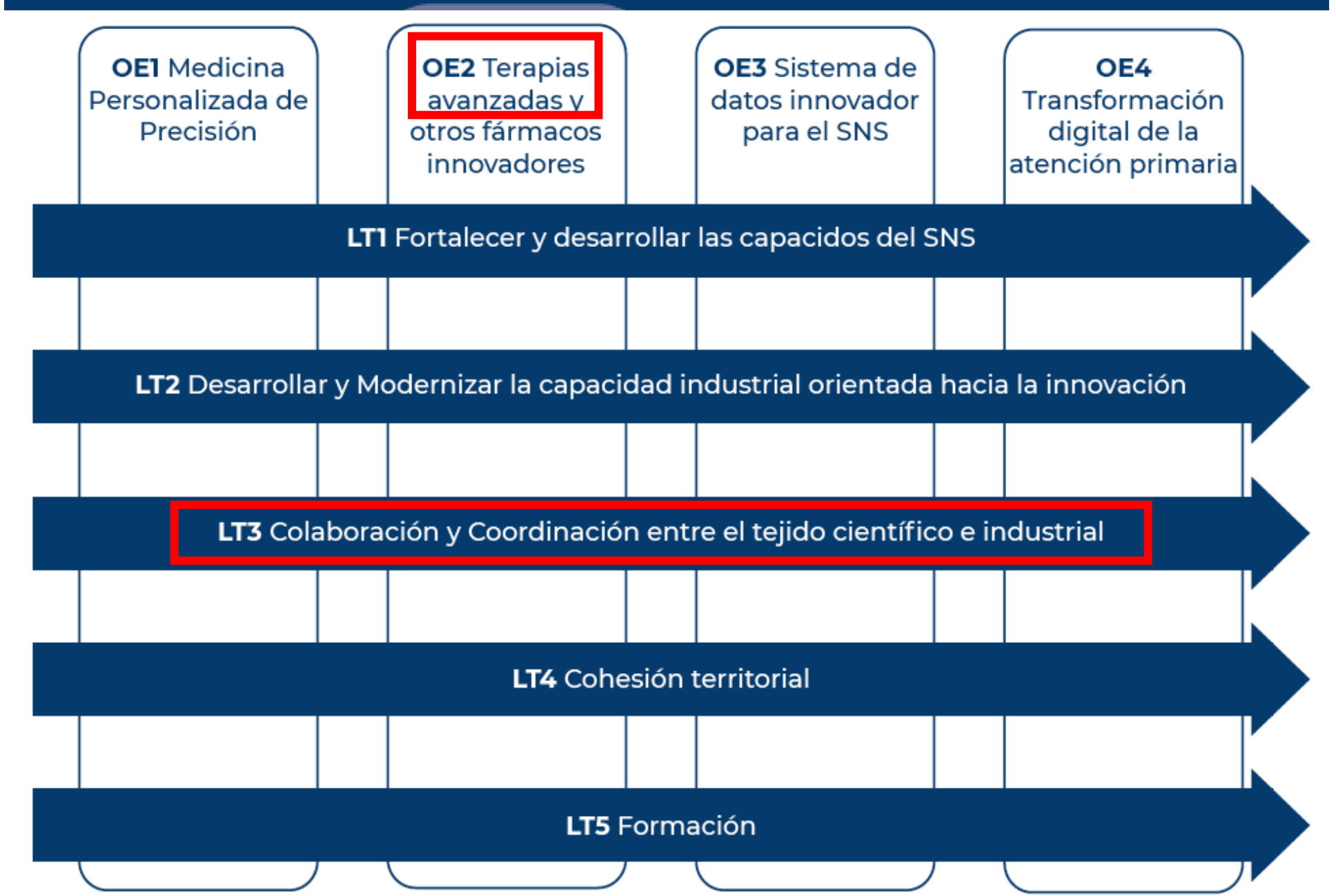


MINISTERIO
DE SANIDAD, CONSUMO Y
BIENESTAR SOCIAL

MULTIDISCIPLINARIDAD

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


OE1 Medicina Personalizada de Precisión
OE2 Terapias avanzadas y otros fármacos innovadores
OE3 Sistema de datos innovador para el SNS
OE4 Transformación digital de la atención primaria
LT1 Fortalecer y desarrollar las capacidos del SNS
LT2 Desarrollar y Modernizar la capacidad industrial orientada hacia la innovación
LT3 Colaboración y Coordinación entre el tejido científico e industrial
LT4 Cohesión territorial
LT5 Formación

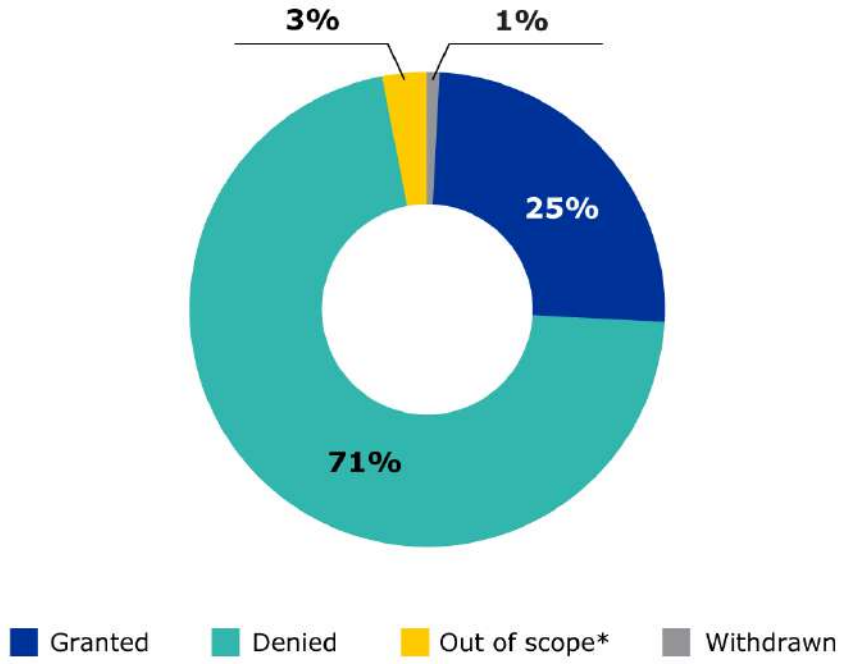
”Hospital Exemption” … and next step

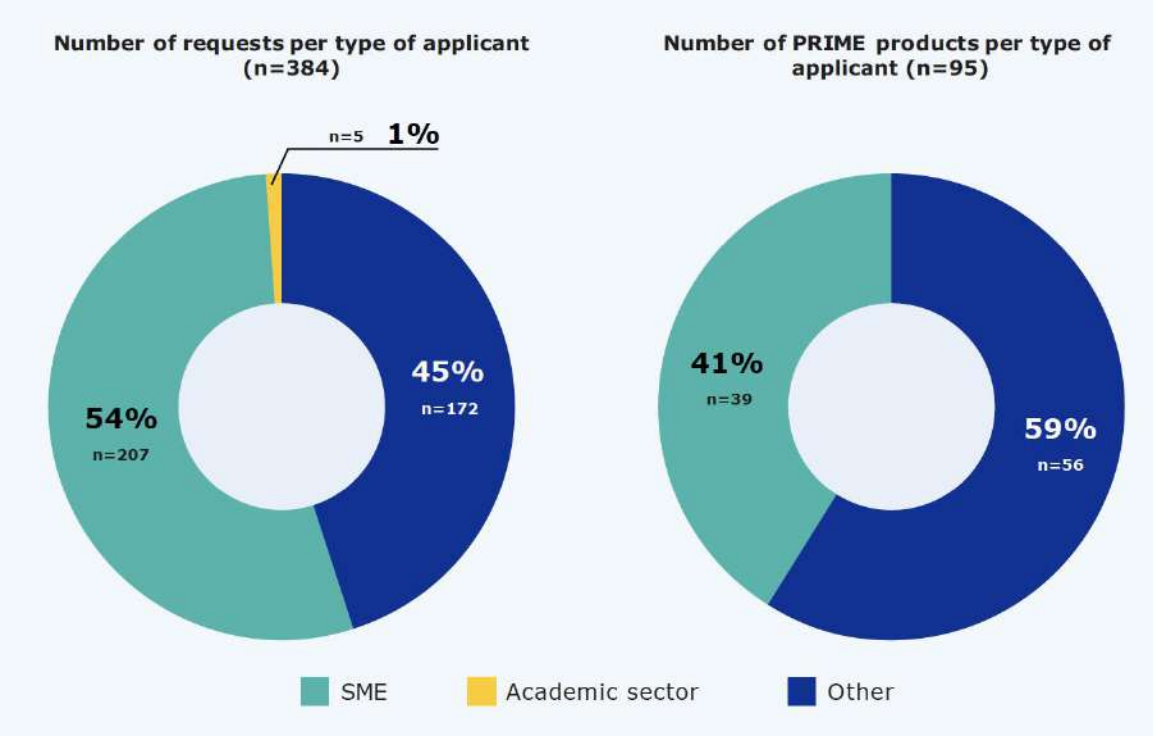
- “HE” as a tool for academic use … intermediate step (Spain):
  - Different rules in different countries, … but which is the purpose?
  - Why not to “spread” the “HE” in different centers?
  - Who can/should decide to “spread” the “best (national) proposal” to different countries? *(patients, regulators, industry, goverments ???)*
- “Market” authorization after “HE” … same pathway/authorization than the ”conventional” pharma process? *(probably the main aspect to be defined should be the “proposal for diffusion/access”).*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRIME:

https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines#list-of-products-granted-eligibility-section





March 2016- **June 2021**,

EUROPEAN MEDICINES AG
SCIENCE MEDICINES H

16 December 2021
EMA/720469/2021
Human Medicines Division

Subject: **Request for eligibility to the PRIME scheme**
ARI-0001 - EMA/PRIME/21/046

With reference to your request dated 19/10/2021 for access to
treatment of patients older than 25 years with relapsed/refr
(ALL), I would like to inform you that the CHMP during its De
your justification and the recommendation from the Committee f

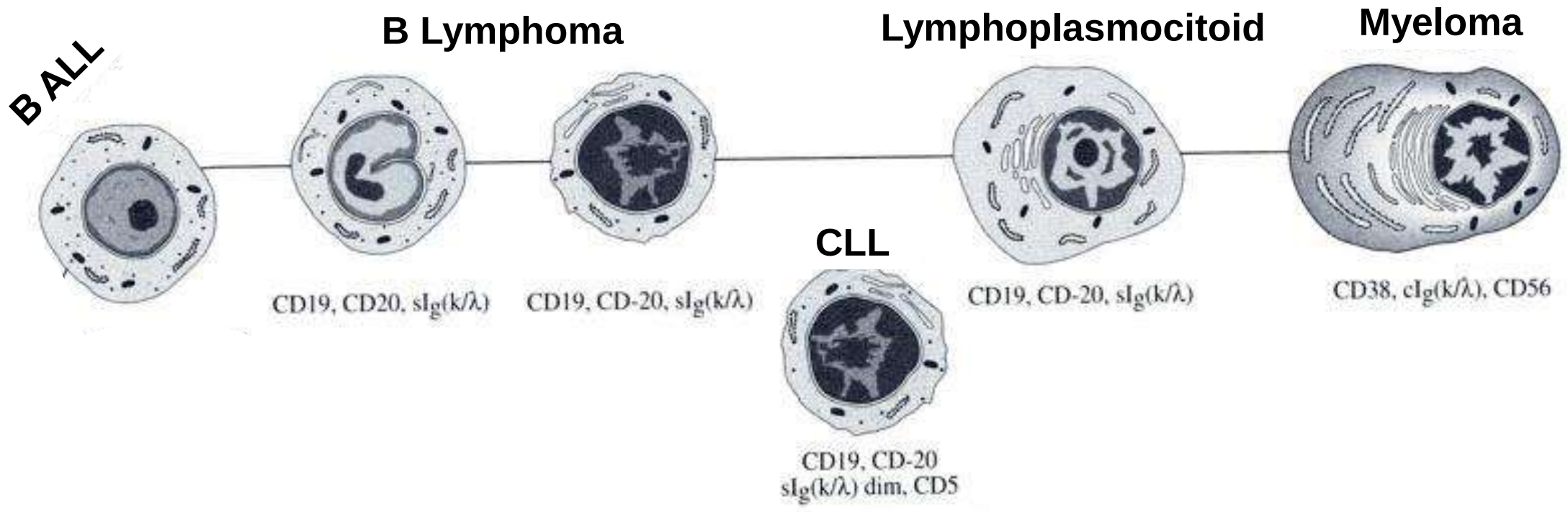
Based on the claims, the justification for such claims and the de
by the applicant, the CHMP is of the view that:

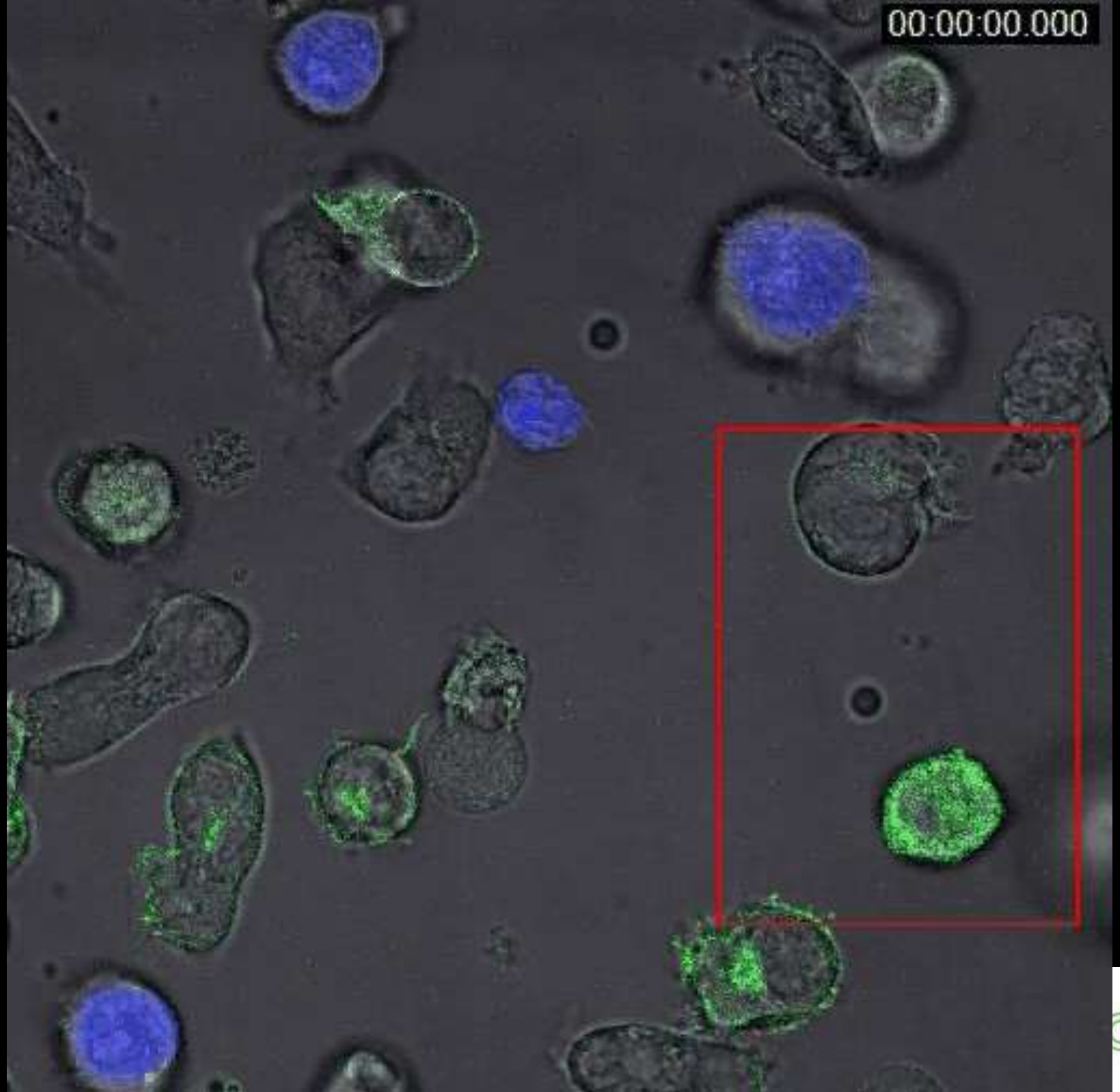
- Despite the availability of a number of treatment options in r
older than 25 years, overall survival is still poor if not followe
cell therapy (allo-HSCT). There is a need for improved therap
patients until transplant, and ultimately improve survival in a
Therefore, an unmet need in the proposed patient populatior
- There is a strong pharmacological rationale for use of ARI-0(

Activity	Status	Comments
Scientific advice for R/R ALL indication	Completed (May 2020)	With the NCA (AEMPS)
Scientific advice for R/R DLBCL indication	Completed (February 2022)	With the NCA (CBG). This trial is sponsored by HOVON
HTA advice	Not planned yet	Discussed with EMA's ATMP office, not considered a priority in view of our academic non-profit status
PIP submission	Planned for Q3 2022	Together with colleagues from other centres (experts in Paediatric Haematology). First draft completed
Orphan designation request	Not planned yet	Possible
ATMP classification	Classified by the NCA (AEMPS) as gene therapy medicinal product (GTMP)	
ATMP certification	Not planned	
Submission of letter of intent	Planned for Q4 2022	
Presubmission meeting with rapporteur	Planned for Q1 2023	
Presubmission meeting with rapporteur	Planned for Q1 2023	
Presubmission meeting with EMA	Planned for Q1 2023	
Request for accelerated assessment	Planned for Q1 2023	
PIP compliance check	Planned for Q1 2023	
MAA submission	Planned for Q3-4 2023	
Invented name request	Planned for Q1 2024	

Access to support through the PRIME scheme is therefore **confirmed**.

CD19 BCMA


B ALL
B Lymphoma
CD19, CD20, sIg(k/λ)
CD19, CD-20, sIg(k/λ)
CLL
CD19, CD-20
sIg(k/λ) dim, CD5
Lymphoplasmocitoid
CD19, CD-20, sIg(k/λ)
Myeloma
CD38, cIg(k/λ), CD56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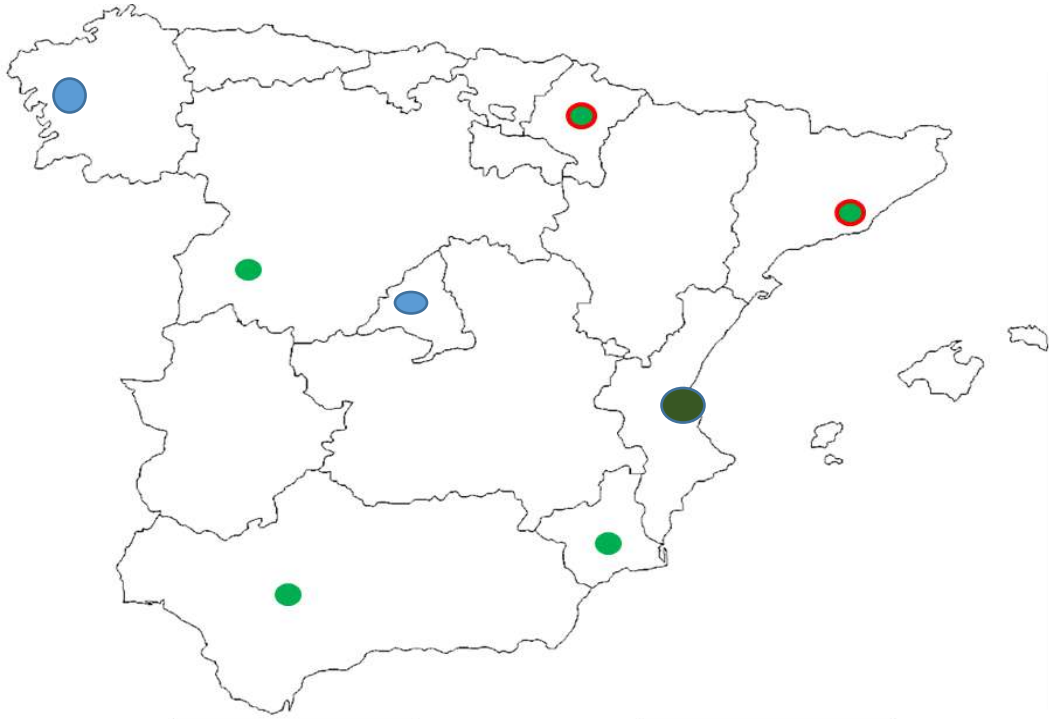
After ARI-0001, ARI-0002h

- Expertise used for another product: ARI-0002h



Clínica Universidad de Navarra

COMPLEJO ASISTENCIAL UNIVERSITARIO DE SALAMANCA

Arrixaca Hospital Universitario "Virgen de la Arrixaca"

Clínic Barcelona

Universitat de Barcelona

IDIBAPS

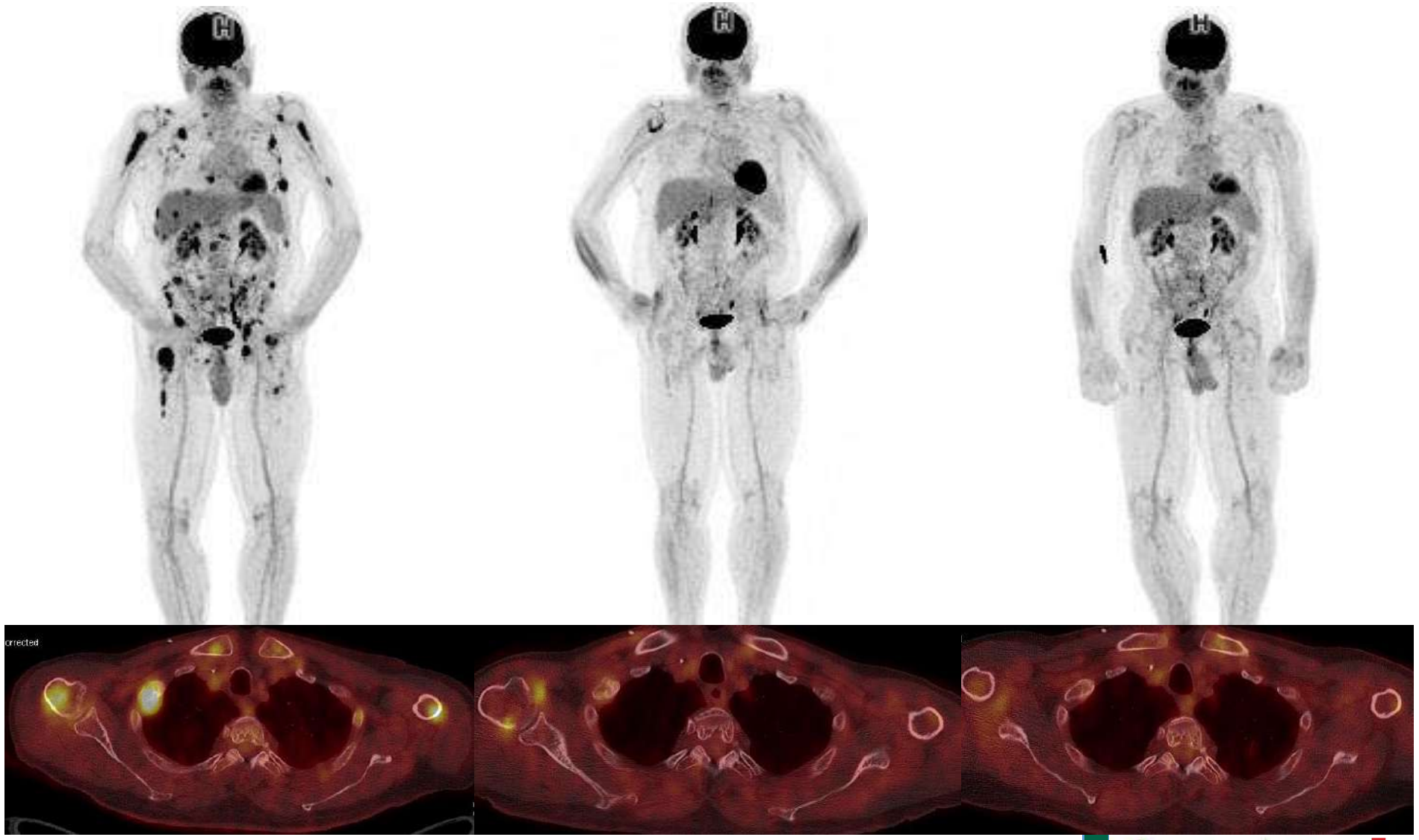
Sant Joan de Déu

Response to ARI0002h

Overall response rate in the first 3 months, n (%)	30 (100%)
Partial response, n (%) Very good partial response, n (%) Complete response, n (%)	6 (20%) 9 (30%) 15 (50%)
Median time to best response, days (95% CI)	99 (29-108)
Overall response rate, n (%)*	30 (100%)
Partial response, n (%)* Very good partial response, n (%)* Complete response, n (%)*	2 (7%) 8 (27%) 20 (67%)

Response of plasmacytomas by PET-CT in a patient treated with ARI0002h.

Baseline **Day 100** **Month 12**



Other projects

Consortium of Spanish Children's Hospitals → varim-cel cells in paediatric ALL (CART19-BE-03Ped trial)

Immuneel India → phase 2 trial evaluating pseudo-var-cel cells in patients with paediatric/adult ALL → ongoing (3 patients infused)

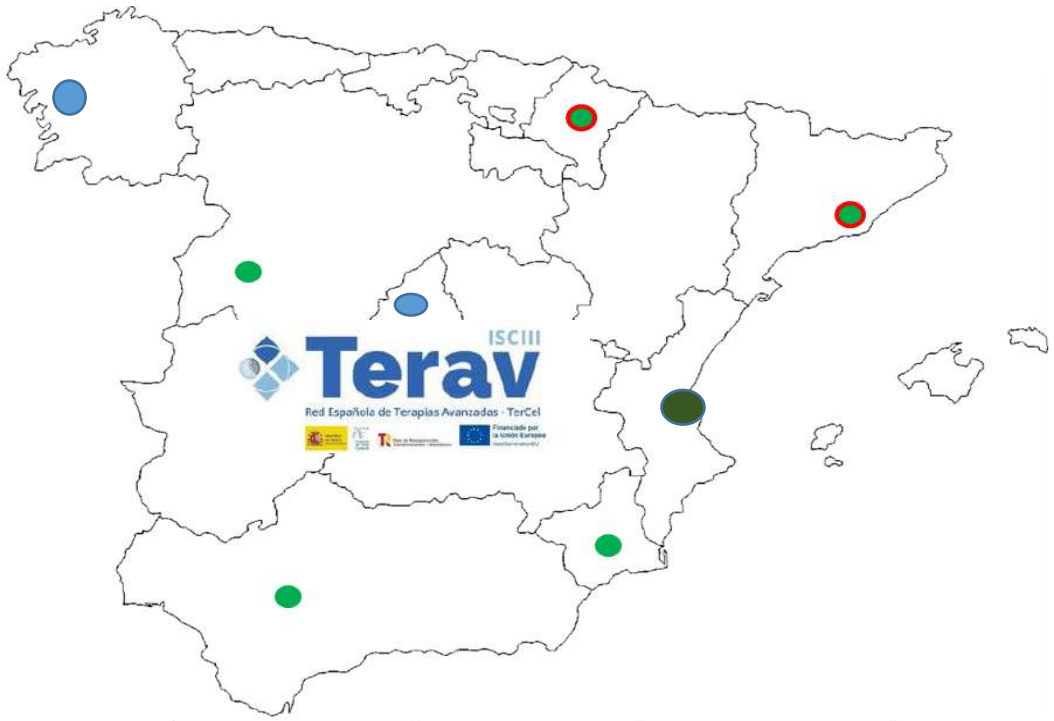
Cellpoint → phase 1 study of pseudo-var-cel in patients with CLL w/o Richter's transformation → ongoing (2 patients infused)

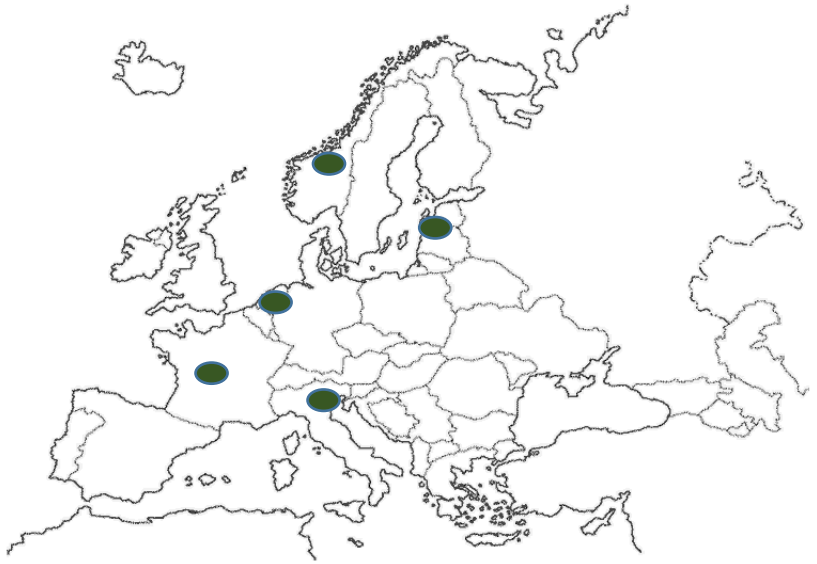
HOVON → non-inferiority trial comparing var-cel to axi-cel/tisa-cel in DLBCL → Scientific Advice submission possible in late 2022

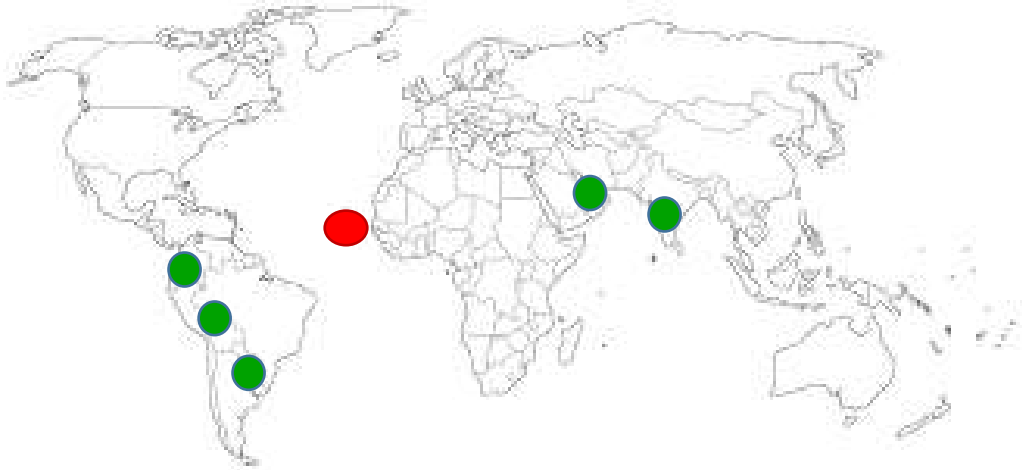
GALARIA → pilot study of **ARI-0003** (dual anti-CD19/anti-BCMA CART-cells) in patients with aggressive CD19+ NHL → additional funding requested in a competitive grant

Colaboraciones internacionales y académicas

Red en España, Europa & Mundo







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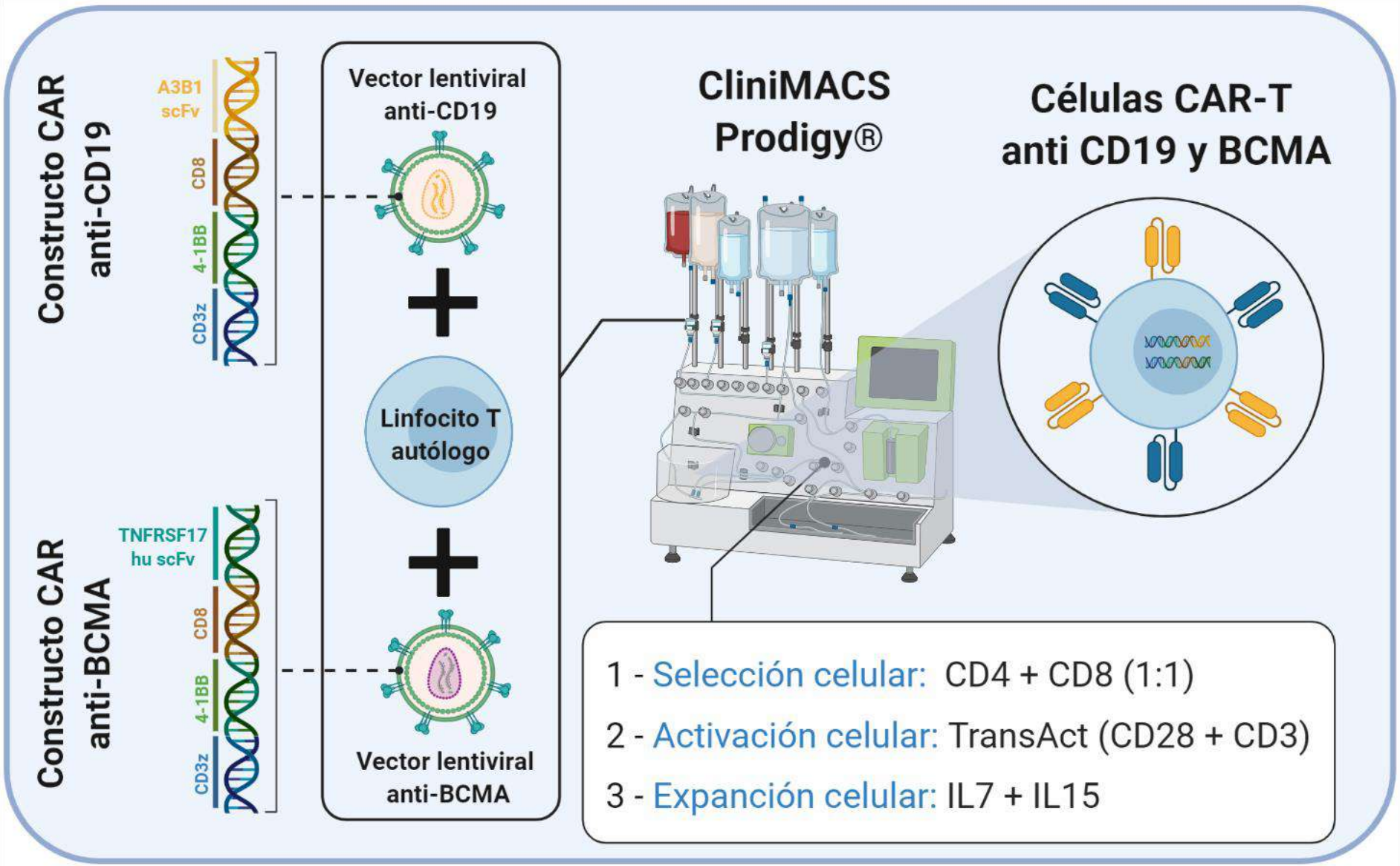
Arrixaca Hospital Universitario "Virgen de la Arrixaca"

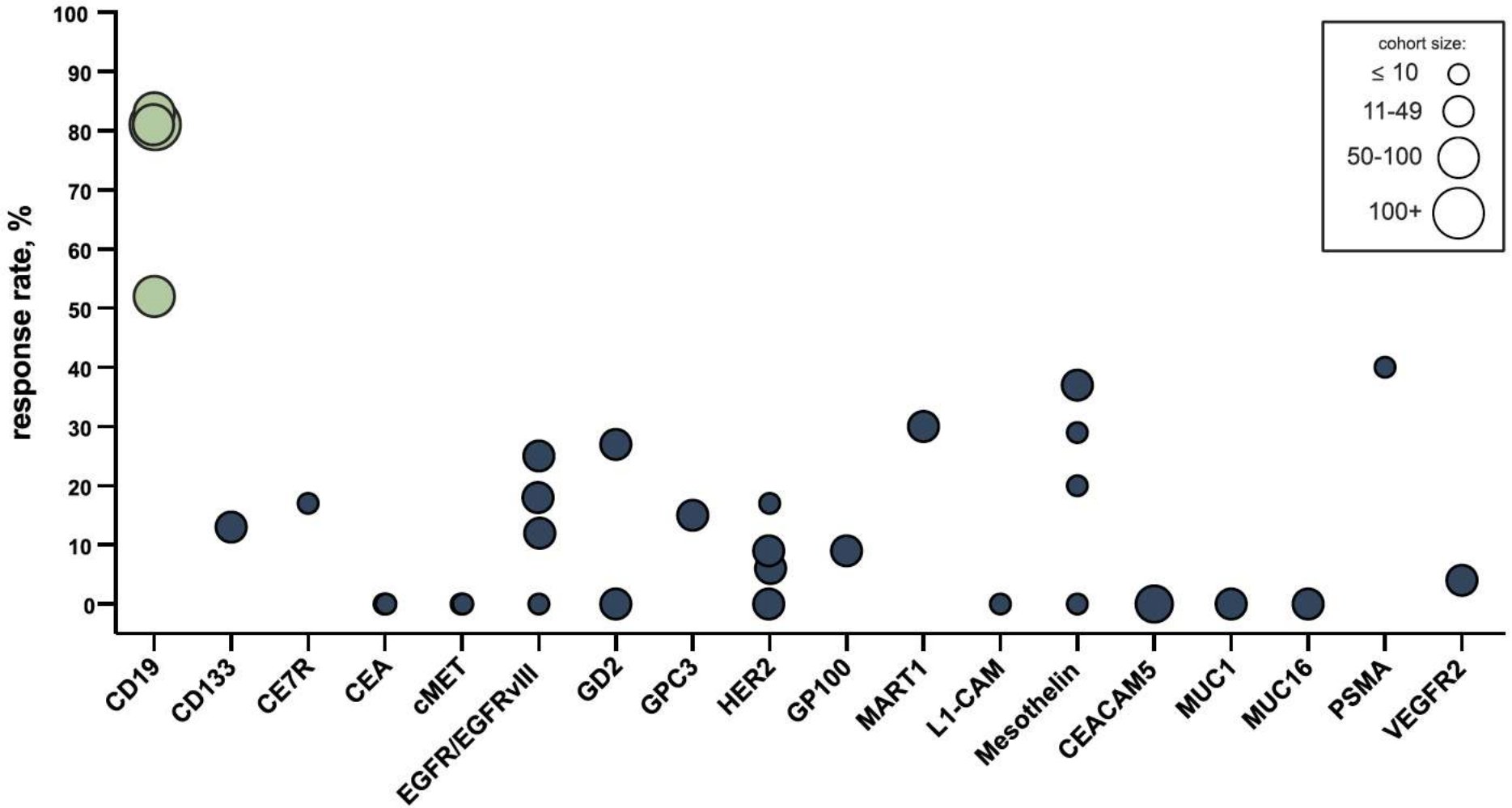
Barcelona

Universitat de Barcelona

Sant Joan de Déu

What is ARI-0003?





Schoenfeld and O'Cearbhaill .The Cancer Journal. 27(2):134-142, 2021

ANTITUMORAL TARGETS (and others) with CAR-T (in HCB/HSJD)

Hematological tumors:

- **CD19** – B-Leukemia & Lymphomas

  Kymriah® o *tisagenlecleucel*,
  Yescarta® o *axicabtagene ciloleucel*,
  Tecartus® o brexucabtagene autoleucel
  Breyanzi® o *lisocabtagen maraleucel*
  ARI-0001 o *varnimcabtagene autoleucel*

- CD269 /**BCMA** – Multiple myeloma

  Abecma® o *idecabtagene vicleucel*
  Carvykti o *ciltacabtagene autoleucel*
  ARI-0002h

- **CD7**, CD1a – T lineage
- **CD123**, **Gya-1,** … , - LMA ….

Solid tumors

- **HER2** (**4D5 variant**)– BC, OC., …
- **IL13Ra** – GBM
- EGFR-viii
- Mesothelin
- **PSMA** – C.P.
- … ….

Autoimmunity, Tx rejection, …

- DSG - Penfigo, …
- **CAAR-HLA_A*2** – rejection, …
- CAR-Treg
- … …

Conclusions & future directions

- ARI-0001 cells showed a safety & efficacy profile that rem ins in line with other (US/EU/Chinese) academic or commercially av roducts. "*Academic-Public product is equivalent*"
- Option for a further safety improvement, u g. "*Possible improvement by Academi-P*
- CART19-BE-01 trial data was s sn Medicines Agency (AEMPS) for Hospital Exe nder the same quality criteria as other drugs *MPs can accomplish quality requirements*"
- A confirma , phase 2 clinical trial for R/R adult ALL patient elopment (CART19-BE-02 trial). *"Hospital Ex nded to other centers (we expect!)" and allow*

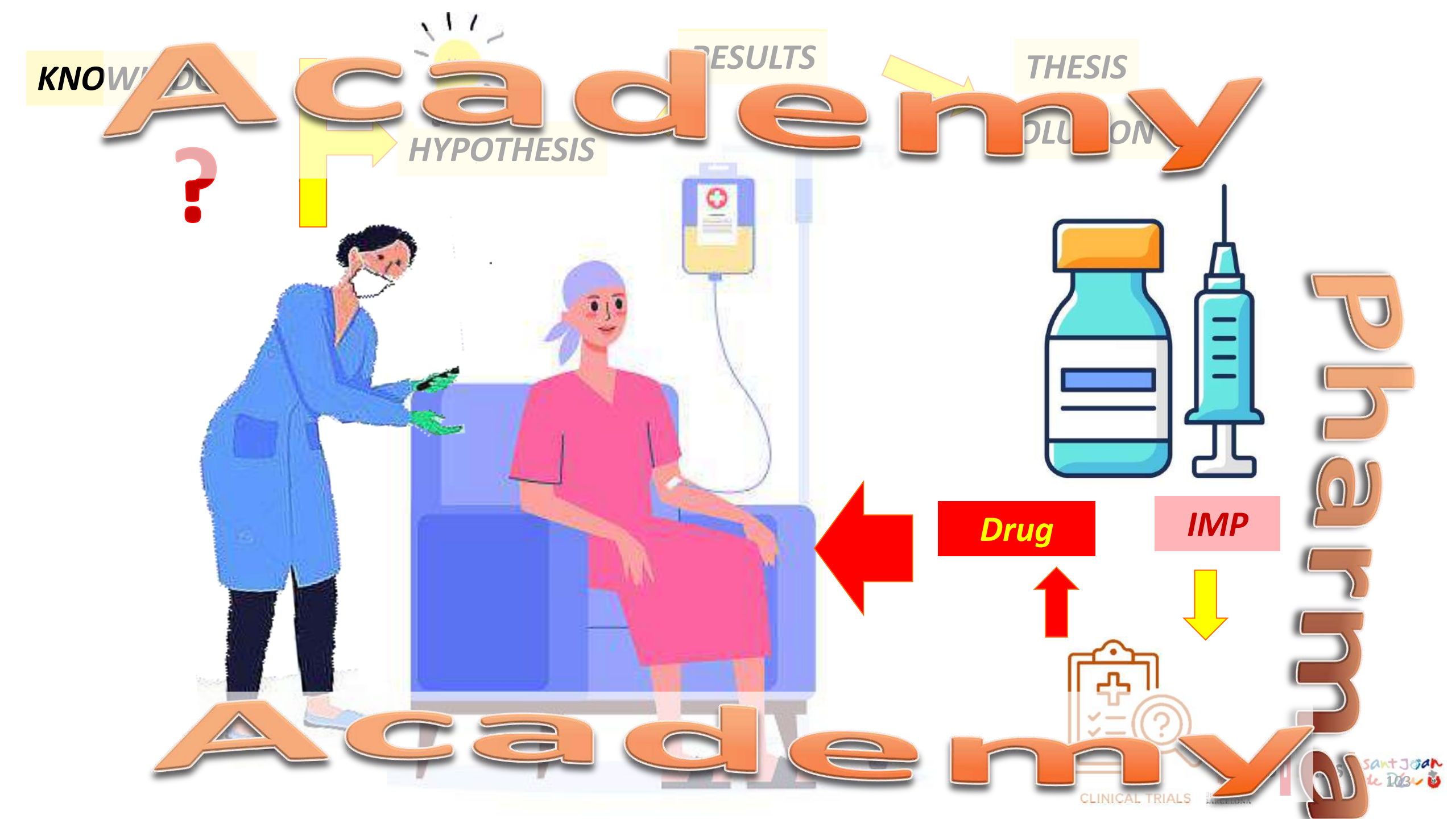
E designation" by EMA

It is possible, if public health systems want to do it

World Exclusive: CAR-T Cell Therapy Successfully Used Against Autoimmune Disease (Medicine)

13 AUG 2021 | JAISRIPADHI | LEAVE A COMMENT

Cocoon bioreactor & Others


KNOW
RESULTS
THESIS
HYPOTHESIS
?
Academy
Drug
IMP
CLINICAL TRIALS
Pharmes

Conclusions

Academic CART-cell development is possible

Requires a change of mentality

Requires help from experts in regulation

Requires stamina → Big Pharma isn't entirely happy with the current situation (e.g. they **dislike** the Hospital Exemption Clause)

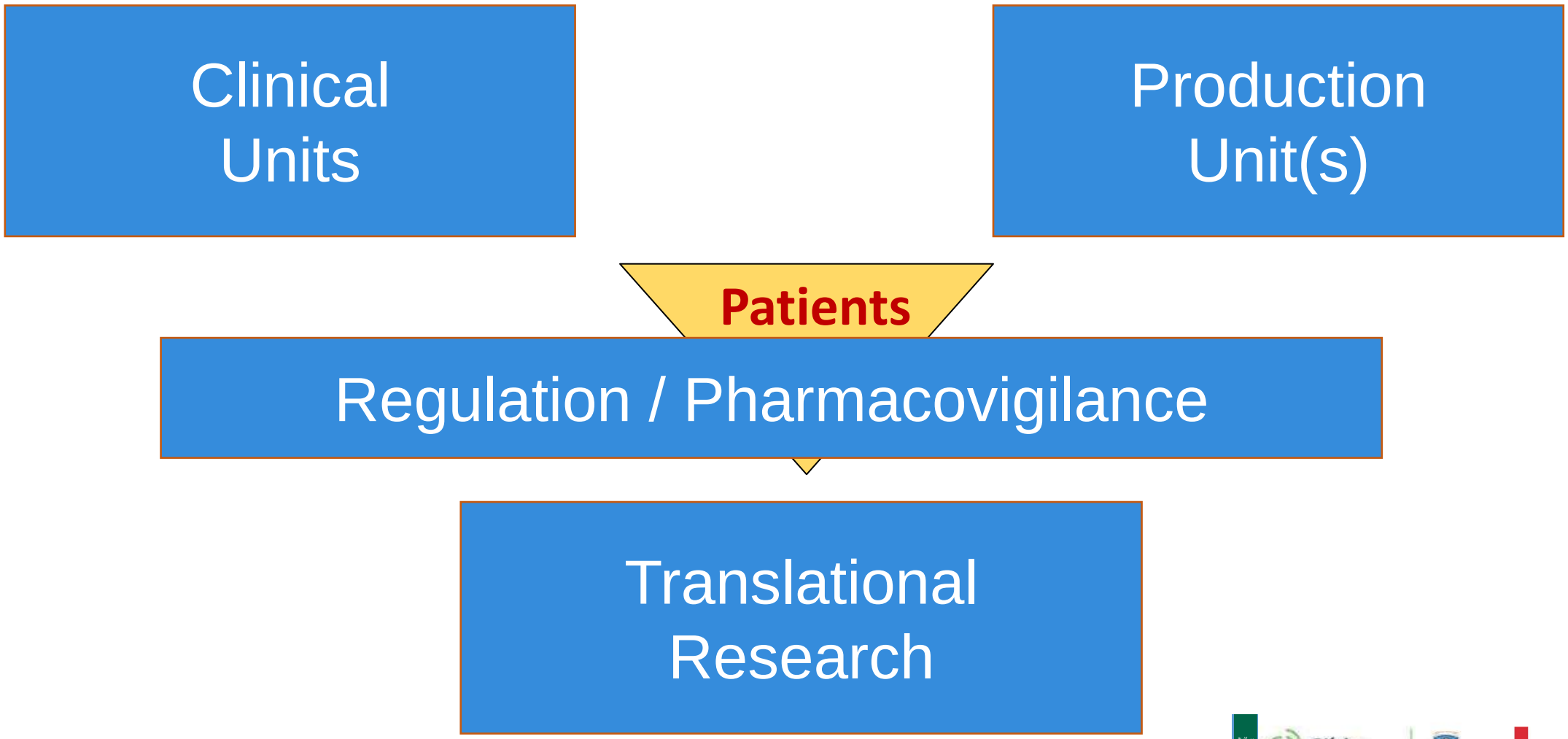
"Where there is a will, there is a way", ... if we are flexible.

National & International Partnerships / collaborations

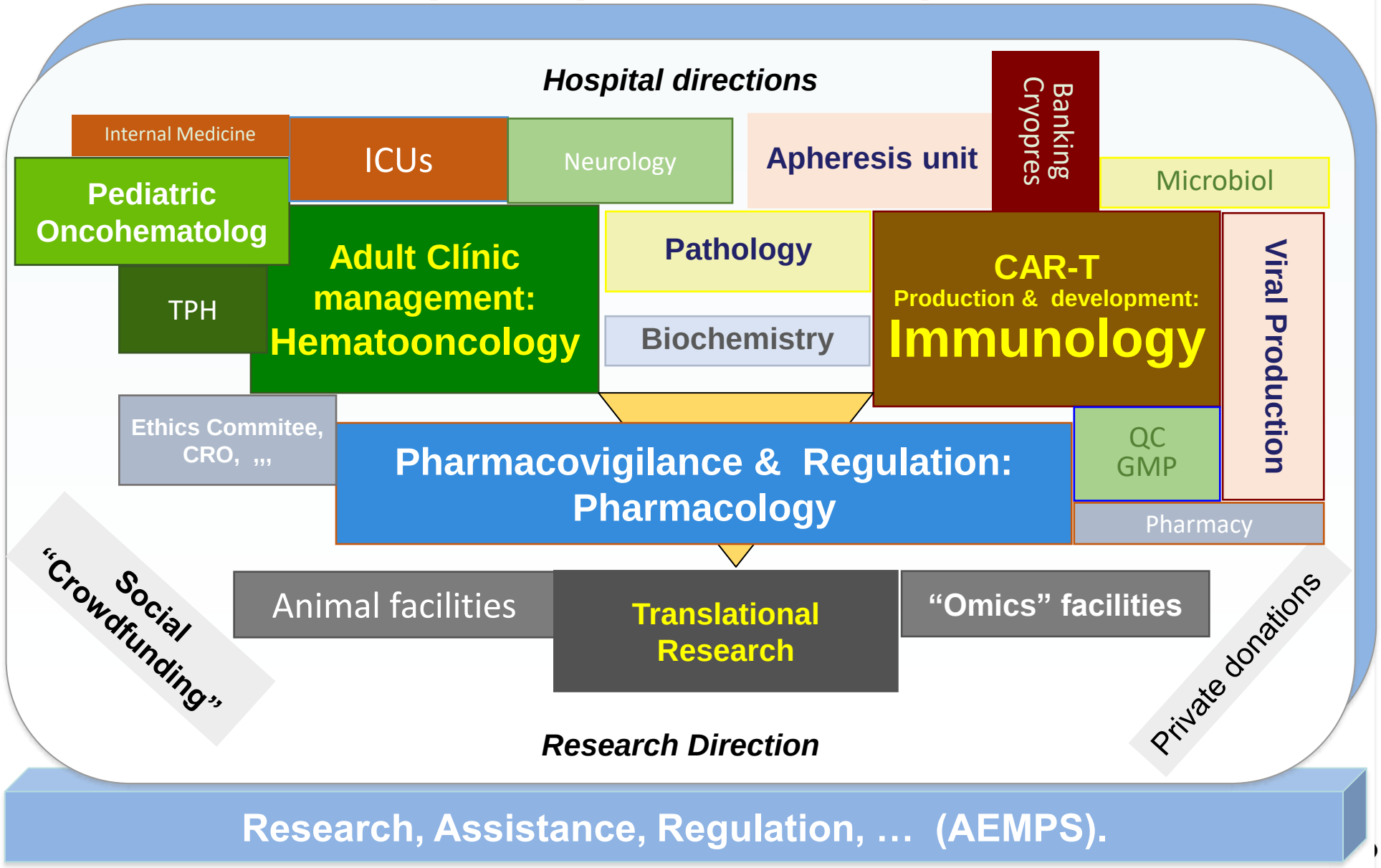
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Slide adapted of the initial proposal of Dr. Delgado

Cell Immunotherapy Unit



How is involved in our “ARI program”? (>200 professionals)



How is involved in our “ARI program”? (>200 professionals)

CLÍNIC
BARCELONA
Hospital Universitari

UNIVERSITAT DE BARCELONA

IDIBAPS

Sant Joan de Déu

Institut de Recerca
CONTRA LA LEUCÈMIA
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· Per la LEUCÈMIA I TRASPLANTAMENTS ·
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Fundació Glòria Soler

Fundación Bancaria
"la Caixa"

NOVARTIS

Roche

isc Instituto de Salud Carlos III

Immunology

Mariona Pascal

Marta Español

E. Azucena González-Navarro

Daniel Benítez, Raquel Cabezón

Natalia Egri, Carlota Garcia-Hoz, Maria Sánchez, Jordi Yagüe

Miguel Caballero, Anna Boronat, Maria Castellà, Hugo Calderón, ... …

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Guillermo Suñé

Beatriz Martín Antonio

Lorena Perez-Amill

Sonia Guedan

Nela Klein,

Elias Campo, …

IJC

Pablo Menéndez

Clara Bueno

Julio Castaño (BST), …

AT Unit

Esteve Trias, Jaime Tabera, …

CTU

Sara Varea, Eulàlia Olesti, Joan Albert Arnaiz, …

Creatio UB

Josep Maria Canals

[illegible] Martínez

[illegible]piñá, ...

Adult Hematology

Julio Delgado

Valentín Ortiz

Carlos Fdez Larrea

Eva Giné

Gerardo Rodríguez

Aina Oliver, Àlex Bataller

Armando López-Guillermo

Jordi Esteve

Álvaro Urbano-Ispizua, ...

Pediatric Hematology (HSJD)

Susana Rives

Anna Alonso

Montse Torrabadell, … …

Oncology

Aleix Prat

Núria Chic, ...

Hospital management

Josep M. Campistol

Antoni Castells

Aurea Mira

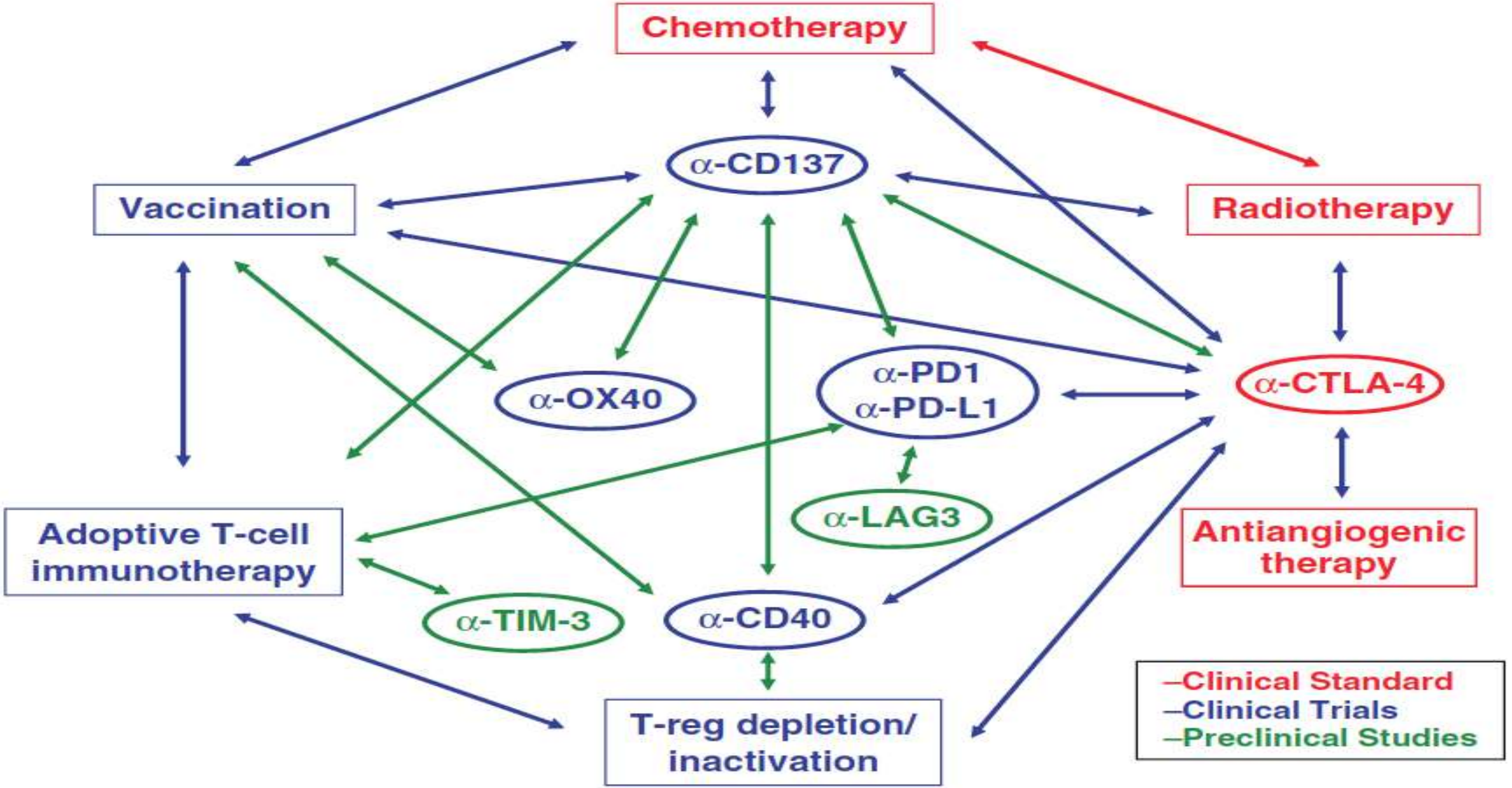
Manel del Castillo

Miquel Pons

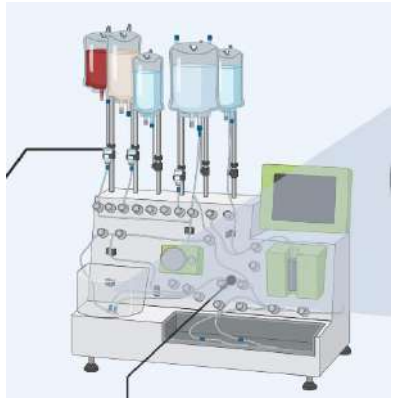
AEMPS

Collaborators:

Upenn, UCLA, BST, 12-O, CUN, HUS, HAM, HUVR, SERGAS-CHUS, HRyC, Ozkaidetza, …



Perez-García JL et al
***Cur Op Immunol** 2014*



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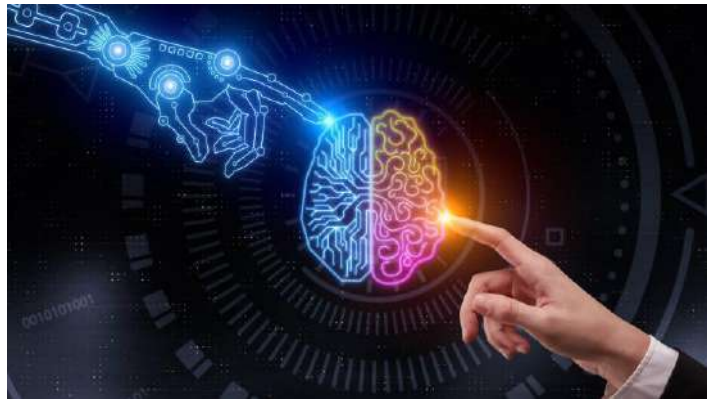
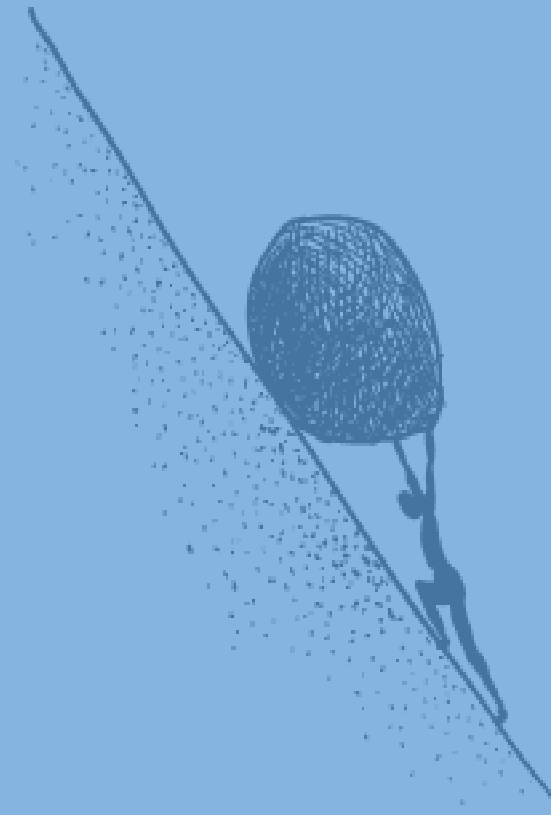
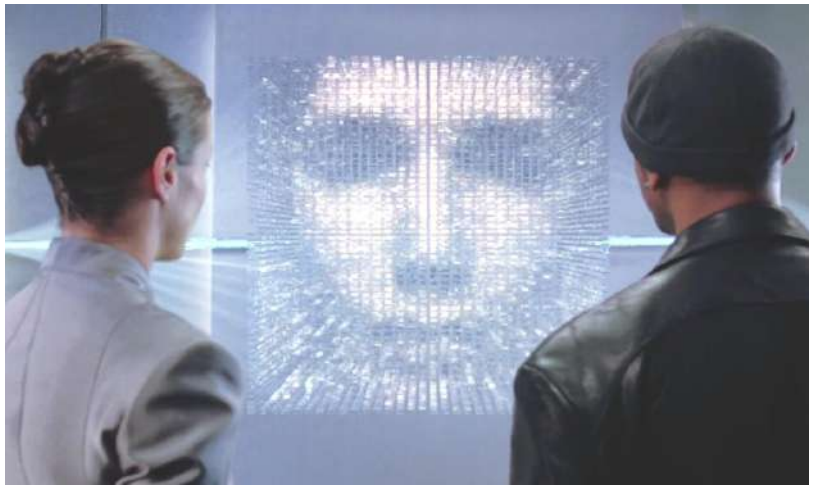
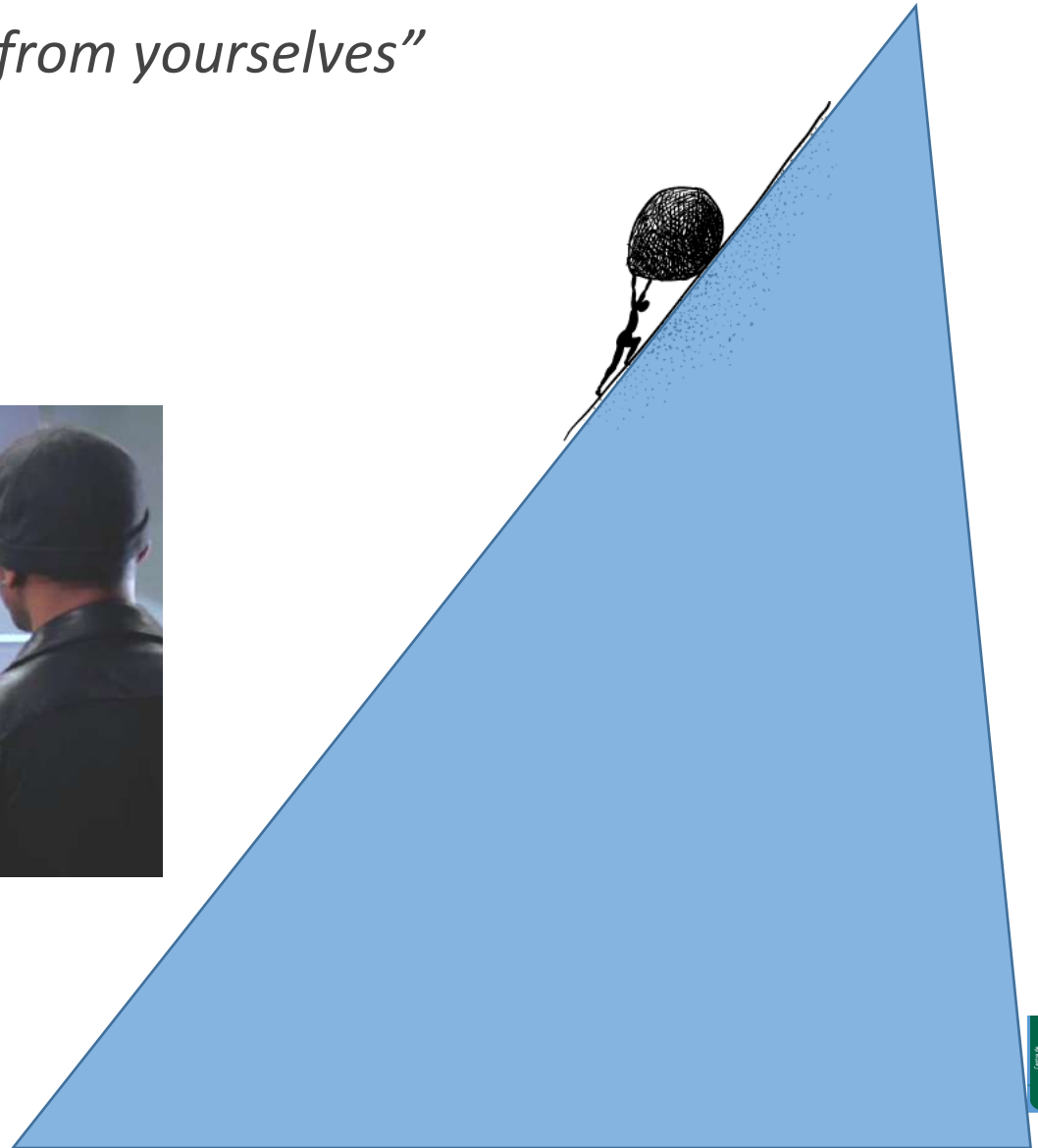


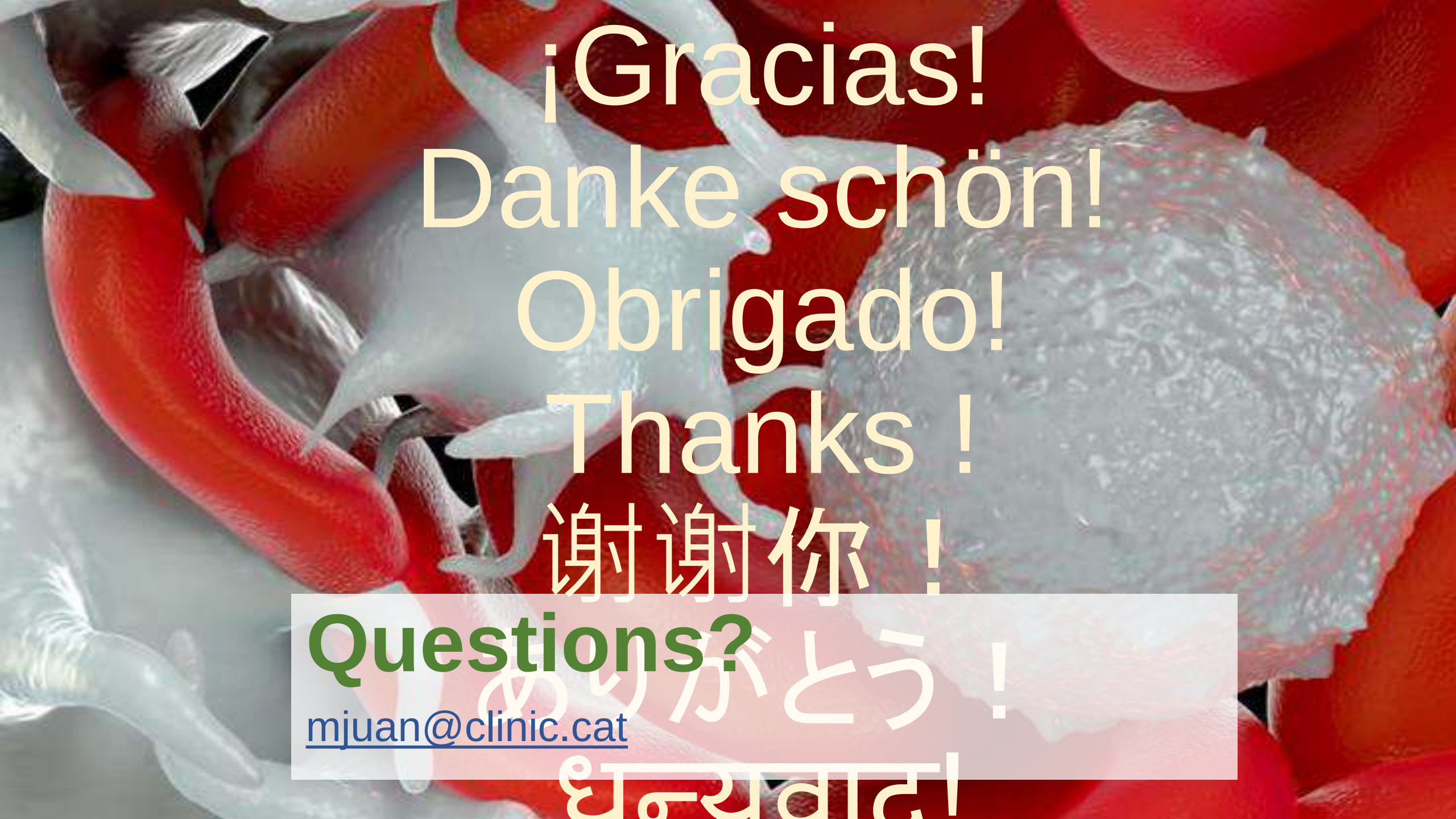


AIDPATH

"Please understand, the regulation is *all that guide me. To protect* ATMPs *some* options *must be sacrificed. To ensure your future, some* patients *must be surrendered. We* DAg./Pharma? *ensure mankind's continued existence. You are so like children. We must save you, from yourselves"*







Questions?

mjuan@clinic.cat