CAR T-CELL THERAPIES

Scientific and Policy perspectives

WEBINAR

5 December 2017

16:00-17:30 CET

ECL
Association of European Cancer Leagues
Access to Medicines Task Force

European Alliance for
Responsible R&D and Affordable Medicines

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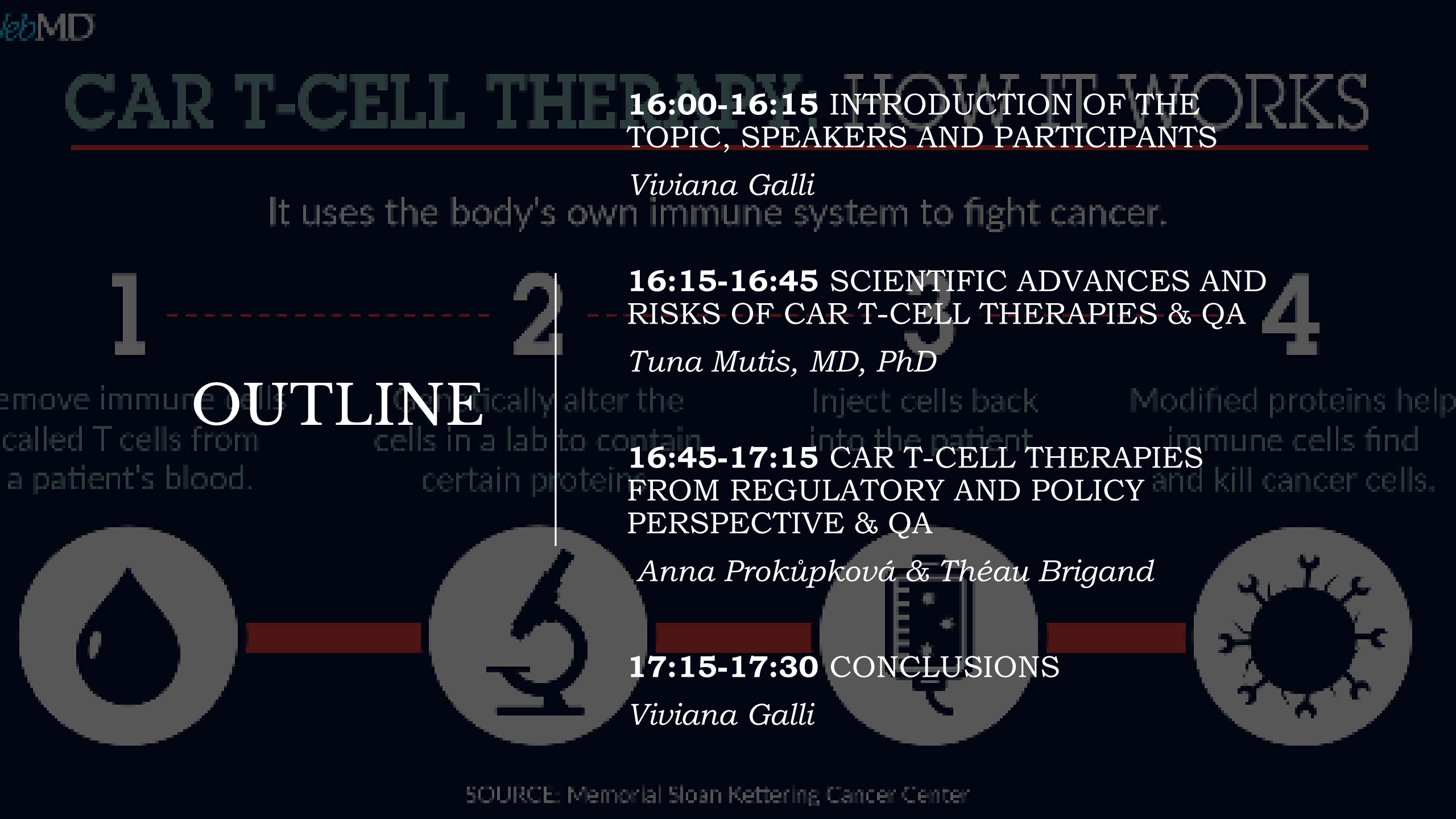


OUTLINE

16:00-16:15 INTRODUCTION OF THE TOPIC, SPEAKERS AND PARTICIPANTS

Viviana Galli

16:15-16:45 SCIENTIFIC ADVANCES AND RISKS OF CAR T-CELL THERAPIES & QA

Tuna Mutis, MD, PhD

16:45-17:15 CAR T-CELL THERAPIES FROM REGULATORY AND POLICY PERSPECTIVE & QA

Anna Prokůpková & Théau Brigand

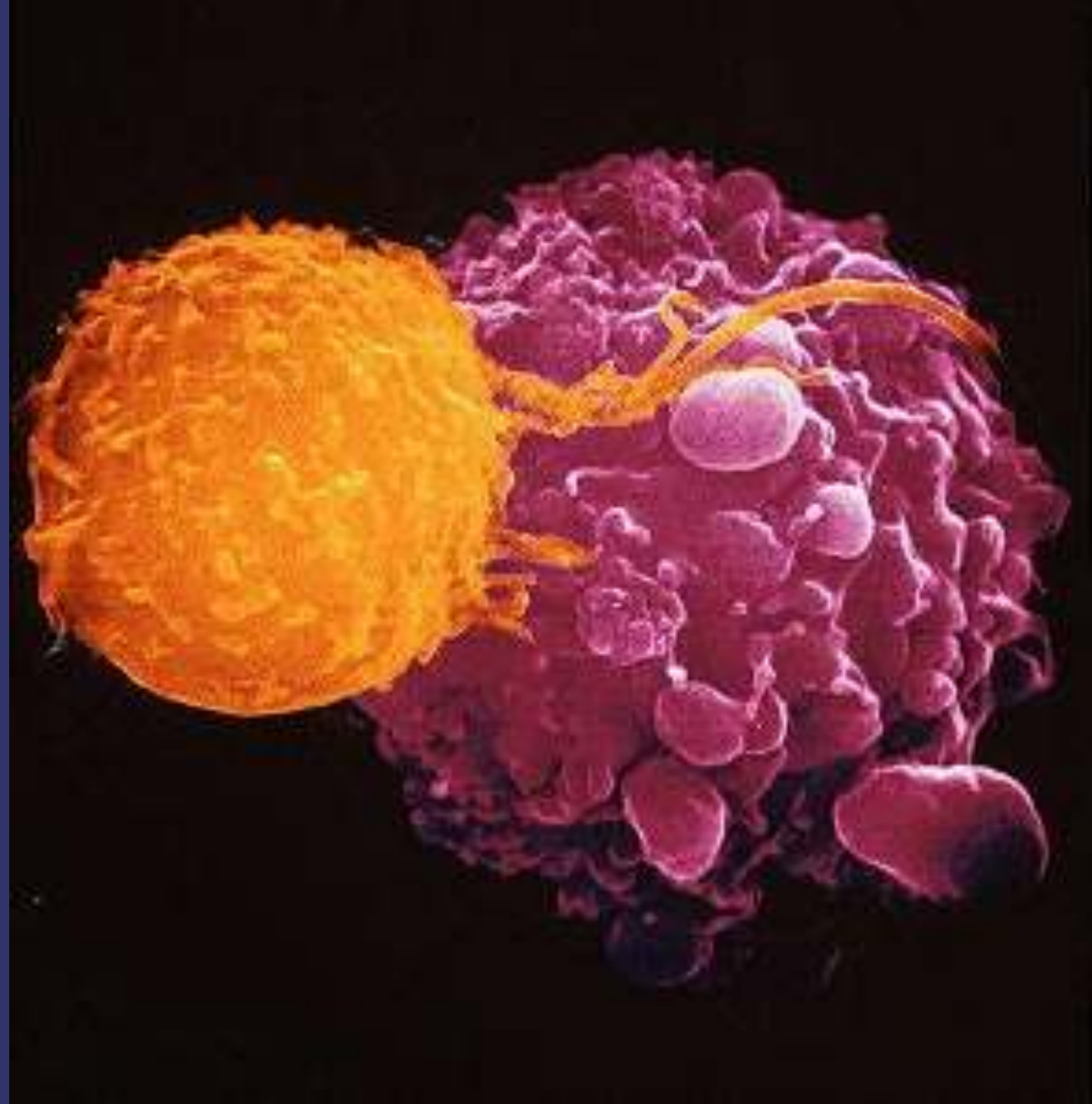
17:15-17:30 CONCLUSIONS

Viviana Galli

CAR T-CELL THERAPIES

Scientific Advances and Risks

Tuna Mutis, MD, PhD
Department of Hematology, VU University Medical Centre Amsterdam



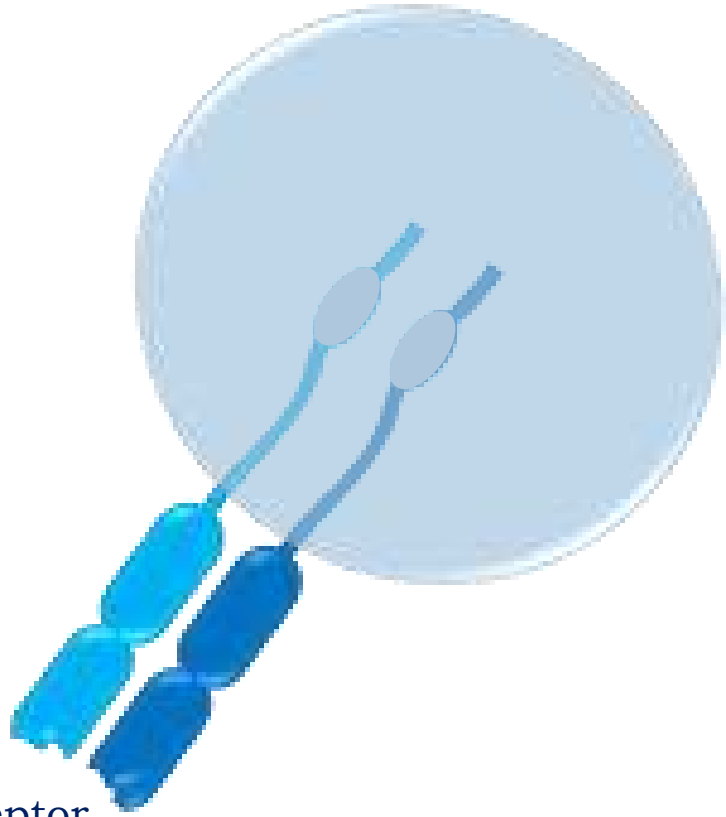
HOW OUR IMMUNE SYSTEM RECOGNIZE AND ELIMINATE TUMORS?

B cell Immunity

Antibody (B cell receptor)

B cells produce the antibody in a soluble form

T cell Immunity



T cell receptor

T cell receptor is not soluble

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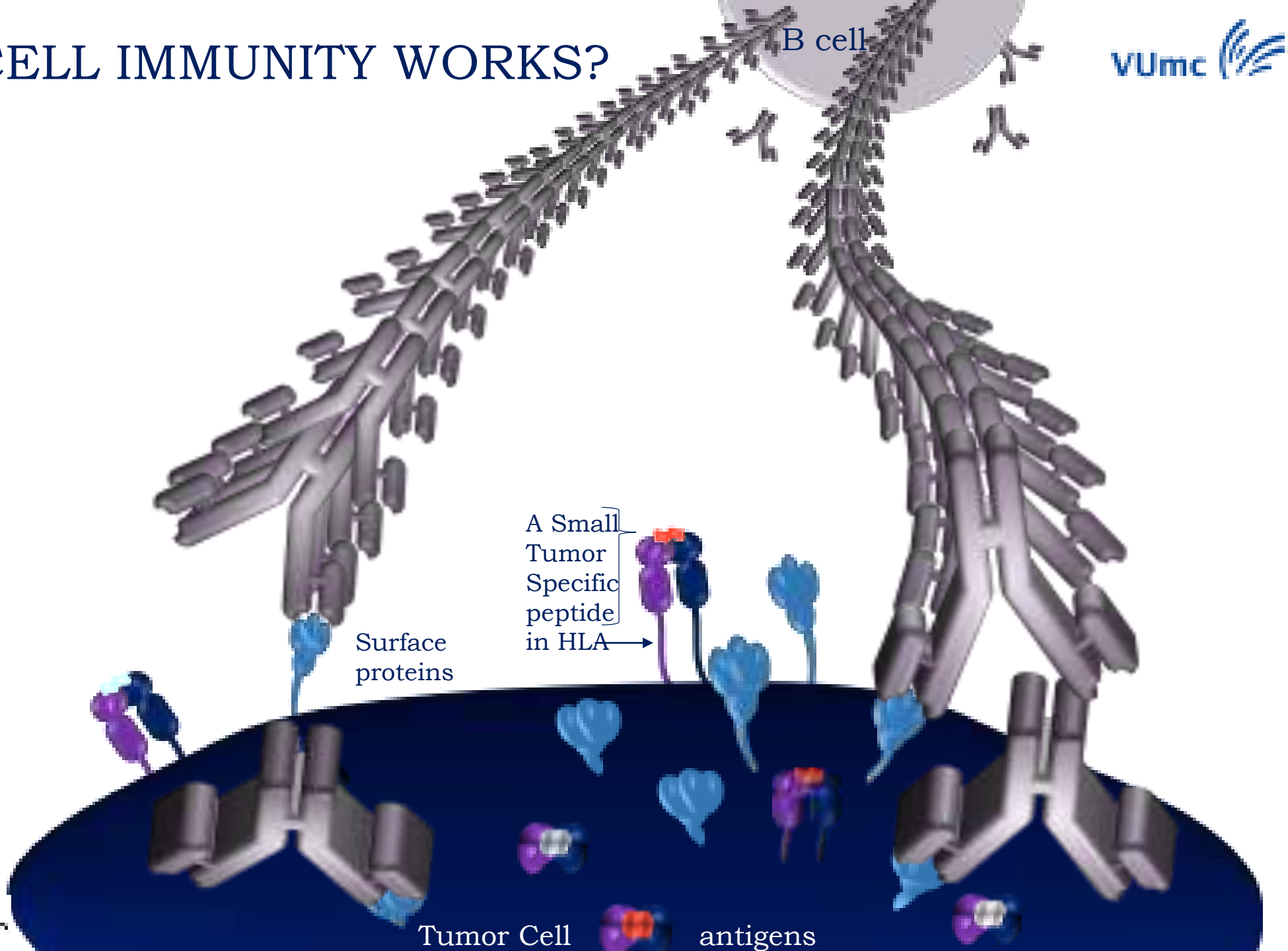
VUmc VU University Medical Center Amsterdam

HOW B CELL IMMUNITY WORKS?



ANTIBODIES GUIDE KILLER CELLS TO FIND AND KILL TUMORS

European Alliance for

T CELLS SEEK TUMORS WITH THEIR RECEPTORS TO KILL THEM

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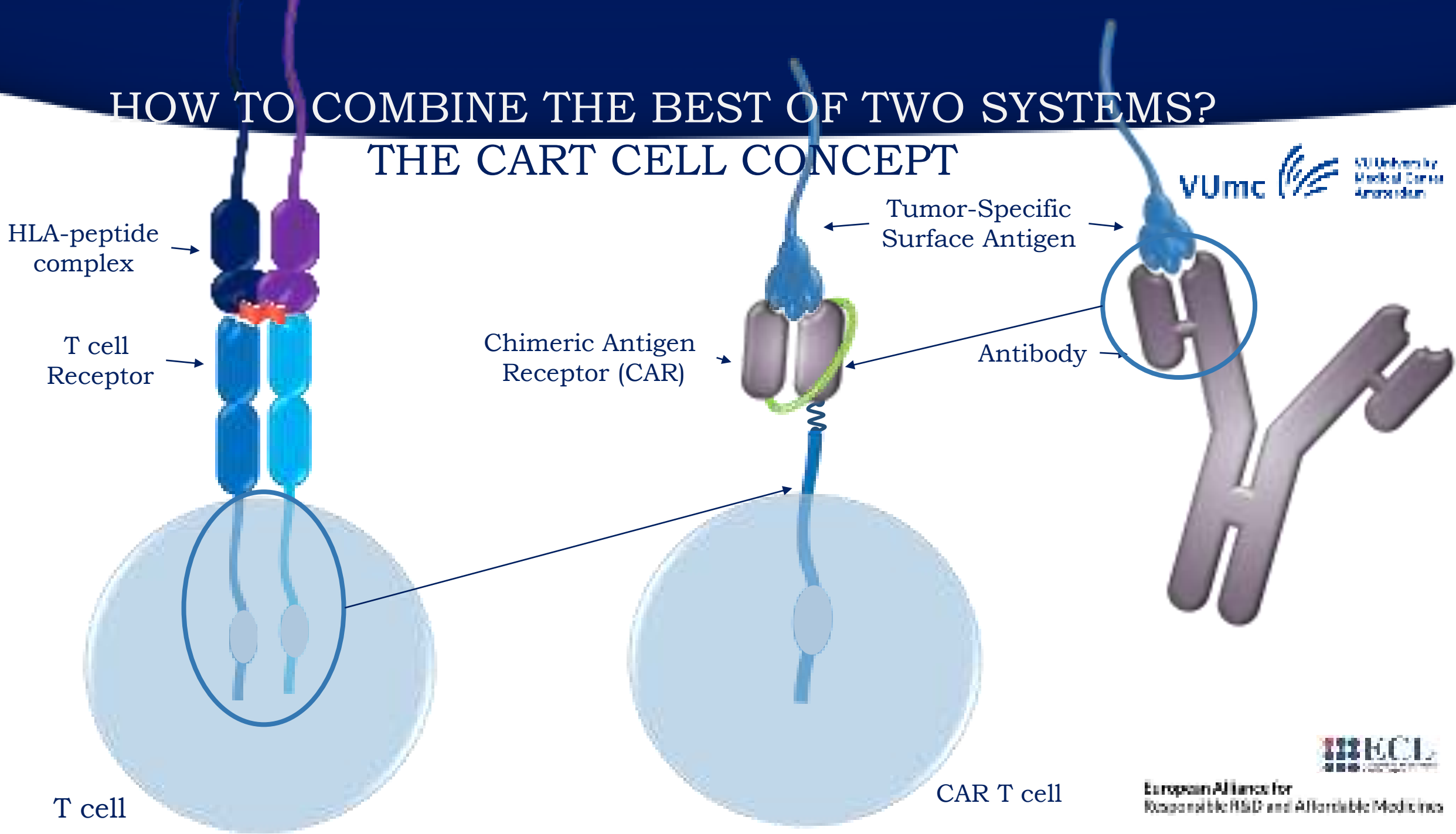
HOW TO COMBINE THE BEST OF TWO SYSTEMS?

THE CART CELL CONCEPT



HOW TO ENGINEER A CART CELL

CAR protein

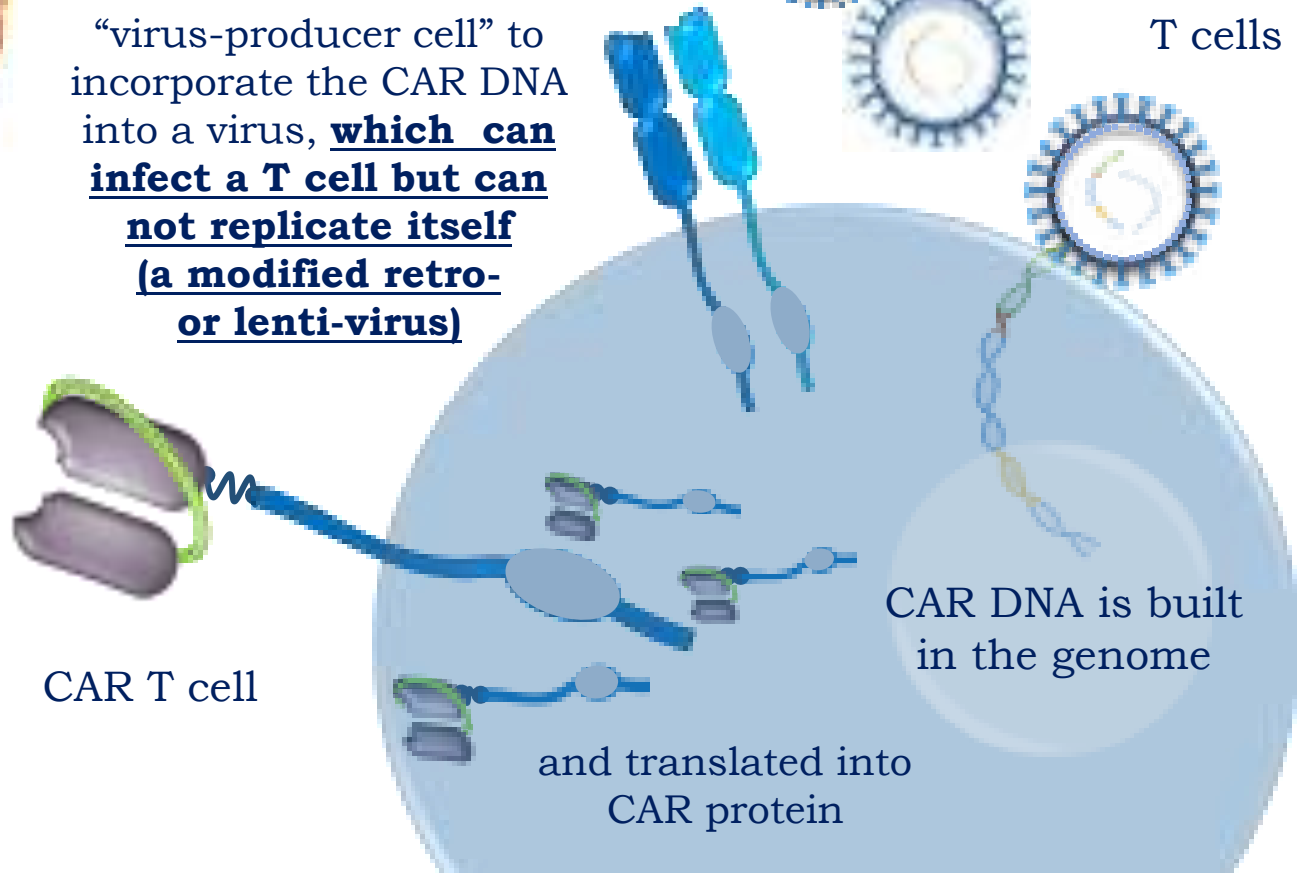
Engineer the CAR DNA

Build CAR DNA in a carrier vector

Insert the vector in a "virus-producer cell" to incorporate the CAR DNA into a virus, **which can infect a T cell but can not replicate itself (a modified retro- or lenti-virus)**

Produce replication deficient virus with the CAR DNA

Infection of T cells



CAR T cell

CAR DNA is built in the genome

and translated into CAR protein

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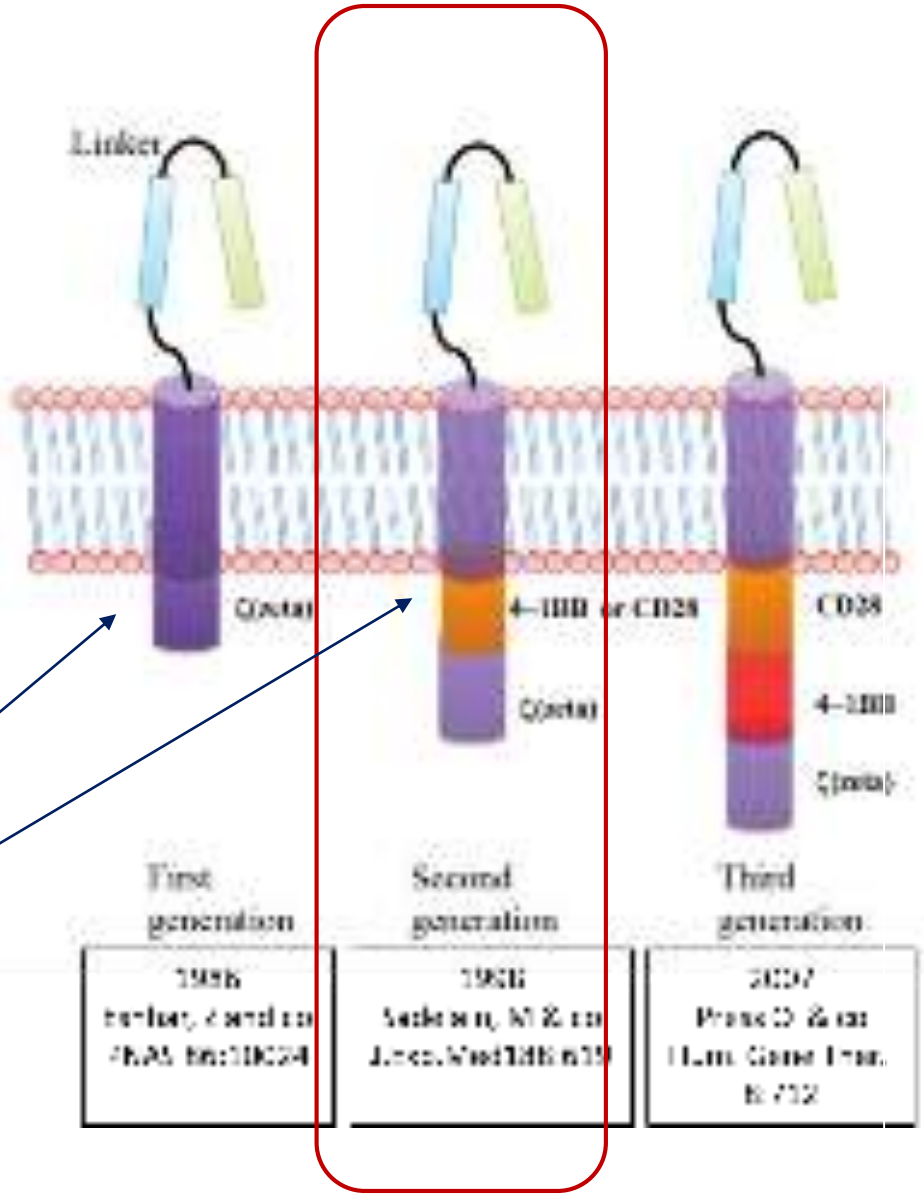
CAR DESIGNS



First activation signal

Co-activation signal

Nomenclature:
Targeted Surface molecule
(eg: CD19, CD38, BCMA)
+ CART

Scientific papers also mention the type of stimulatory chain
(eg: 28z or BBz)
Then

CD19-CART (-28z)

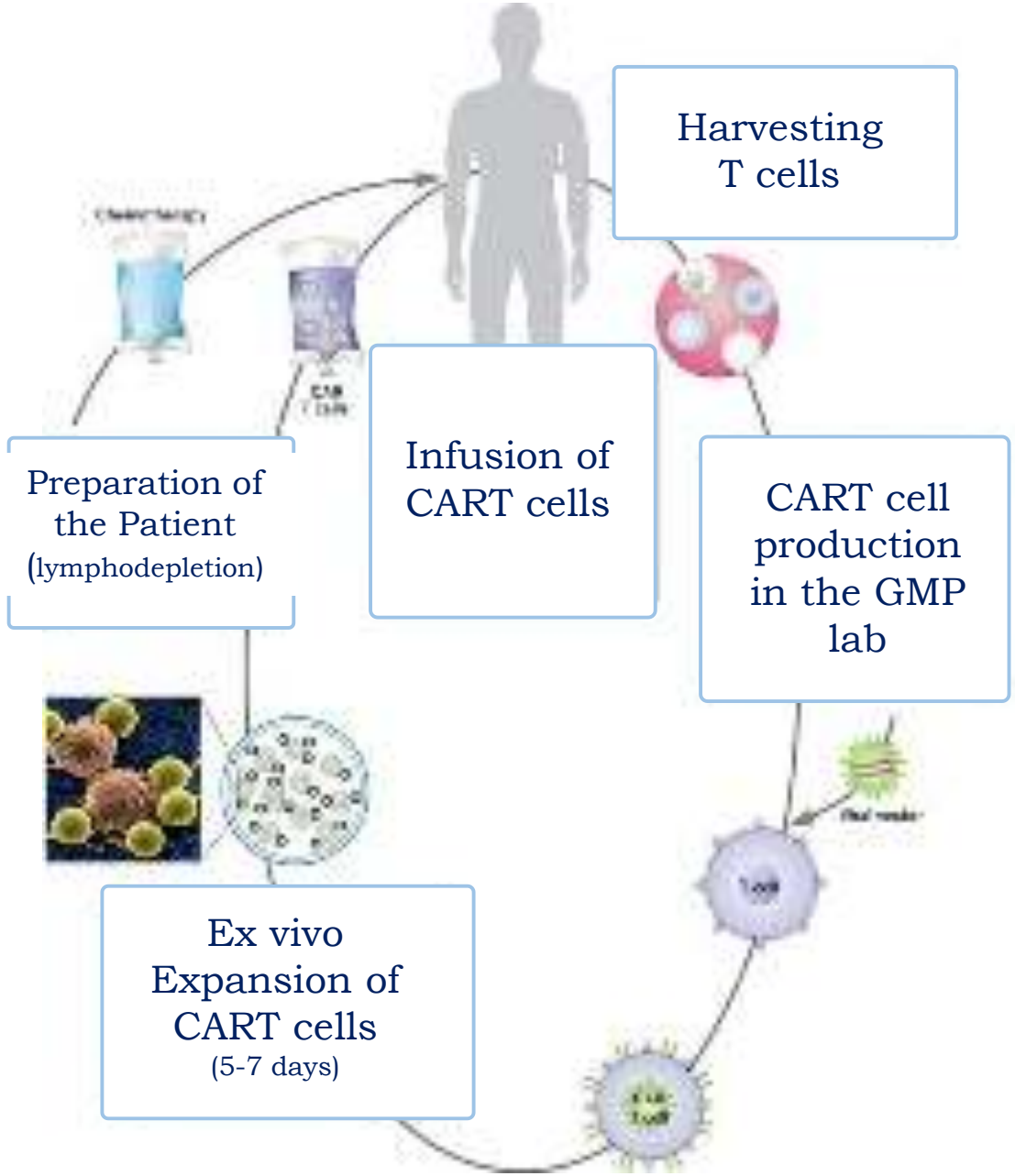
BCMA-CART (-BB1z)

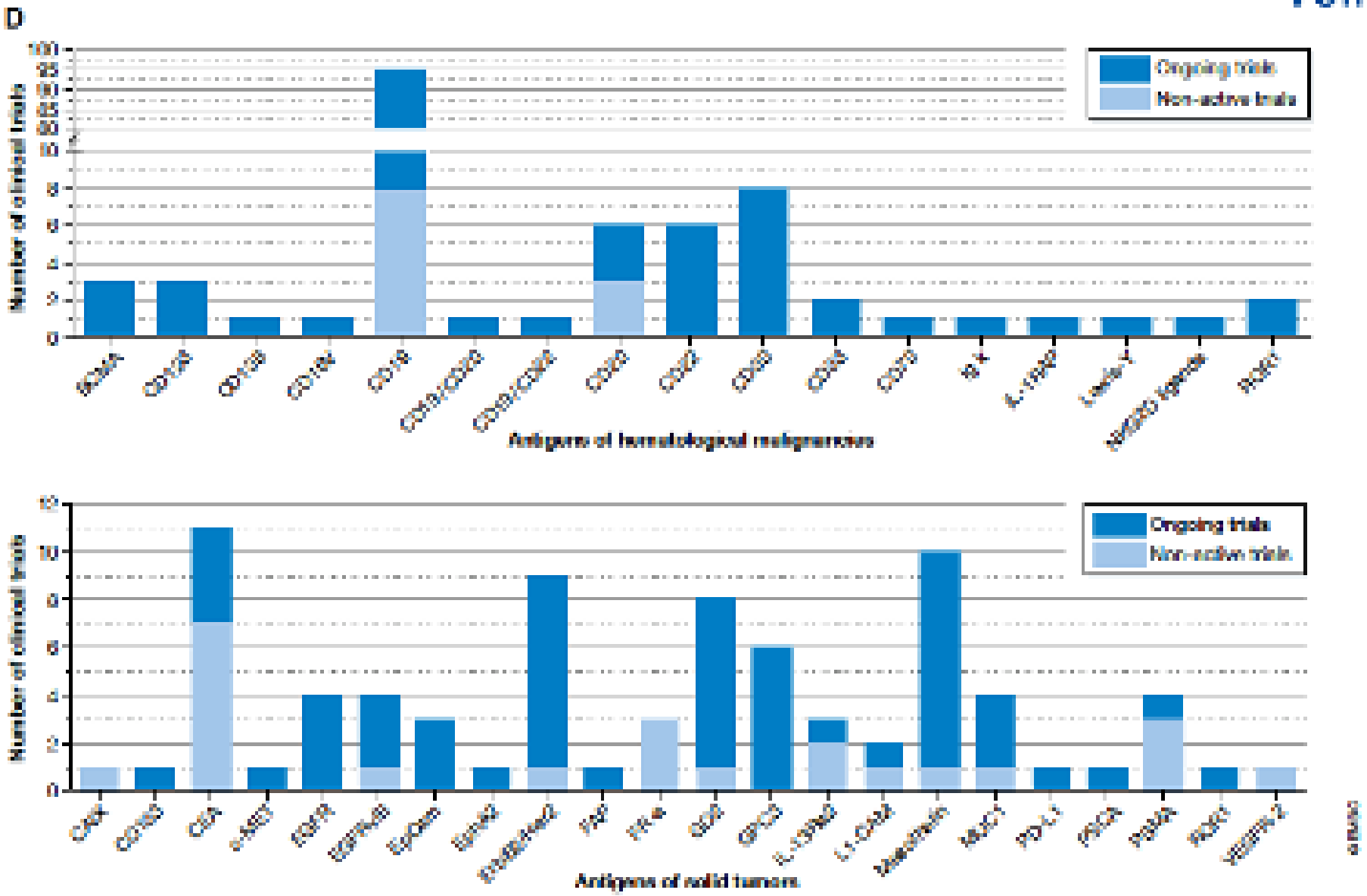
NB: there are different antibodies with the same target specificity
but with different potencies.

Thus the same name (eg: BCMA-CAR) may refer to different CART cells.
Hence, the
clinical efficacies may be different.

The same holds true for costimulatory domains
(CD28z vs 41BB)

IMMUNOTHERAPY WITH CAR T CELLS





Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts J.Hartmann Et al.

DOI 10.15252/emmm.201607485| Published online 01.08.2017EMBO Molecular Medicine (2017) e201607485

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Table 1 | **CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL**

Institution	CAR design	Patient population	Outcome	Toxicities	Reference
MSKCC	CD28, CD3ζ	• n = 17 adults • R/R B-ALL	91% CR	• B-cell aplasia • CRS	NCT01044069 [REF. 14]
UPenn/ CHOP	4-1BB, CD3ζ	• n = 30 children and young adults • B-ALL	90% CR	• B-cell aplasia • CRS	NCT01626495 [REF. 15]
NCI	CD28, CD3ζ	• n = 20 children and young adults • B ALL	70% CR	• B cell aplasia • CRS	NCT01593696 [REF. 17]
Fred Hutchinson	4-1BB, CD3ζ	• n = 70 adults • B-ALL	83% CR	CRS	NCT01865617 [REF. 19]

Preconditioning chemotherapy was used in all the trials shown in this table. B-ALL, B-cell acute lymphoblastic leukaemia; chemo, chemotherapy; CHOP, Children's Hospital of Philadelphia; CR, complete response; CRS, cytokine-release syndrome; Fred Hutchinson, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; R/R, relapsed and/or refractory; UPenn, The University of Pennsylvania.

Jackson, H. J. *et al.* (2016) Driving CAR T-cells forward *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.36

1. The First ever FDA approval for a CAR-T cell therapy: Kymriah™ (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice
(Novartis)
Aug 30, 2017

Price tag: $475,000 per patient. "value-based" pricing
(for those patients who go into remission within three months)

2. FDA also approves (CD19) CAR-T cell therapy, YESCARTA™, to treat adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
(Kite Pharma/Gilead)
October 18, 2017

Price tag: $373,000 per patient.

3. FDA Grants BCMA CART-Cell Therapy Breakthrough Designation in Myeloma
Nov 16, 2017
(Blue bird/Celgene)

CART CELLS VS T CELLS

ADVANTAGES	DISADVANTAGES
HLA non restricted: applicable to many patients	Targeting intracellular antigens not possible
No Tumor escape through HLA downregulation, blocked ag-processing	Tumor Escape via - Shedded (soluble) ags, - ag downregulation, - epitope mutation
Targeting non-peptide antigens possible	
Better survival and persistence in the patient due to built-in costimulation	
Better tumor targeting due to high affinity of antibodies and due to higher antigen load	

CART CELLS & T CELLS VS ANTIBODIES

ADVANTAGES	DISADVANTAGES
More potent, due to killer activity of T cells	More Toxic (Both CART cells and T cells (but also bispecific antibodies) can induce deadly Cytokine release Syndrome!)
Long term activity (memory), no need to repetitive weekly or monthly treatments	
Should be relatively cheaper, but…	

CART CELL PROGRAM IN VUmc HEMATOLOGY

Multiple Myeloma

CD38-CART cells

Preclinical-> clinical

BCMA-CART cells

Clinical trial (2018)

Dual-CART cells

Preclinical

Acute Myeloid Leukemia

CLEC12A-CART cells

Preclinical

Dual-CART cells

Preclinical

Universal "Off the Shelf" CART cells

Preclinical

CAR T-CELL THERAPIES

Regulatory and Policy Perspectives

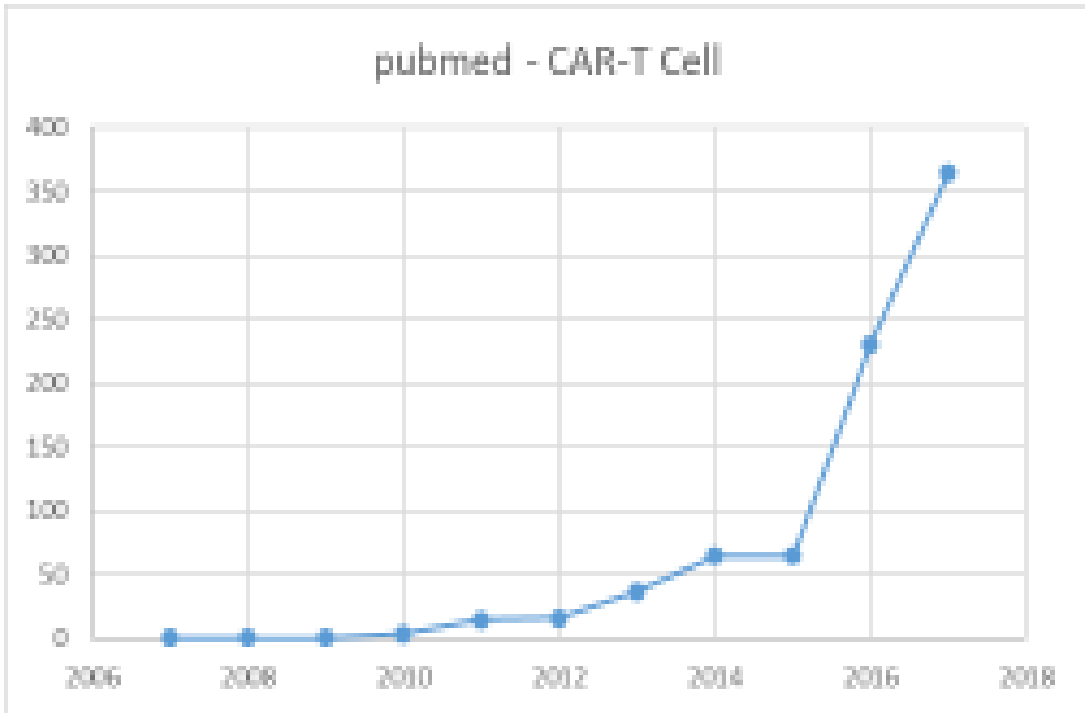
Anna Prokůpková &
Théau Brigand

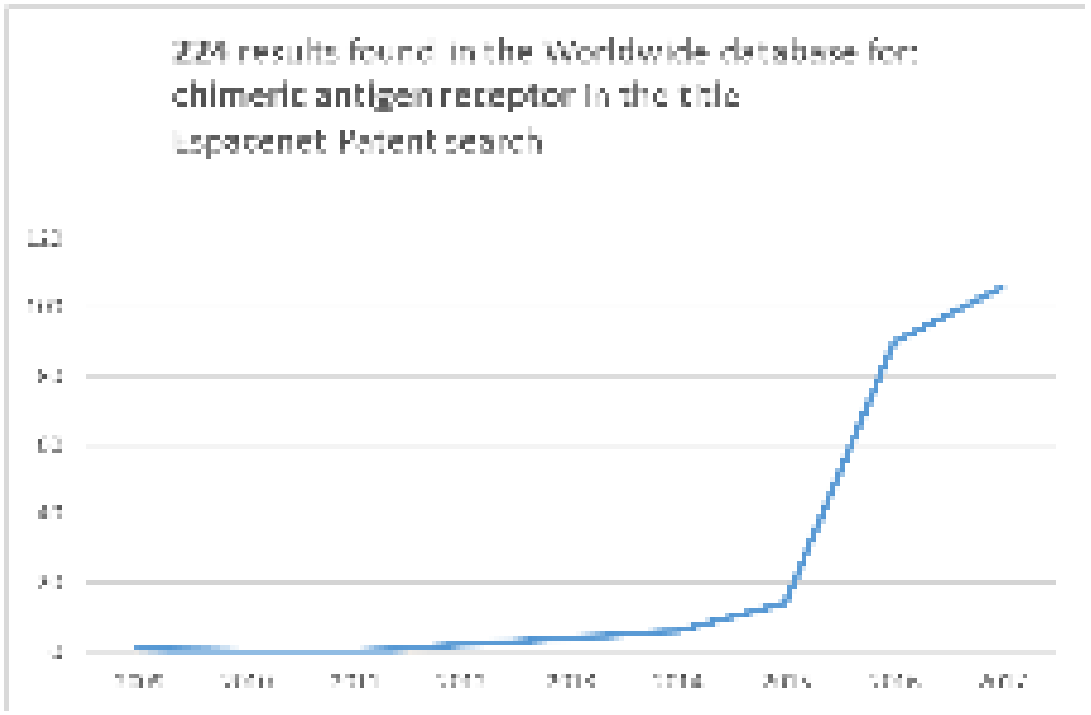
ECL Access to Medicines Task Force

CAR T-CELL THERAPIES: A BRIEF HISTORY

1993	First CAR T-cell developed by Dr. Zelig Eshhar
1996	The first CAR T-cell clinical trial began in 1996 in patients with ovarian cancer
2010-11	Phase 1 clinical trial of CAR T-cells in chronic lymphoid leukemia, two of the three patients achieved complete remission
2012	Emily Whitehead became the first paediatric patient to be treated with CAR T-cell therapy in acute lymphoblastic leukemia (ALL). Highly medialised, her remission helped re-energise a line of underestimated research
2017	The FDA approved the first CAR T-cell therapy, Kymriah®
2017	The FDA approved the second CAR T-cell therapy, Yescarta®
2018	The EMA to approve the first CAR T-cell therapy in Europe

CAR T-CELL, A NEW APPROACH TO TREATING CANCER





2007	1
2008	1
2009	1
2010	4
2011	15
2012	16
2013	37
2014	65
2015	65
2016	231
2017	365

Number of publications on CAR T-cell therapies

Number of patents on CAR T-cell therapies

2009	1
2010	0
2011	0
2012	2
2013	4
2014	6
2015	14
2016	90
2017	106

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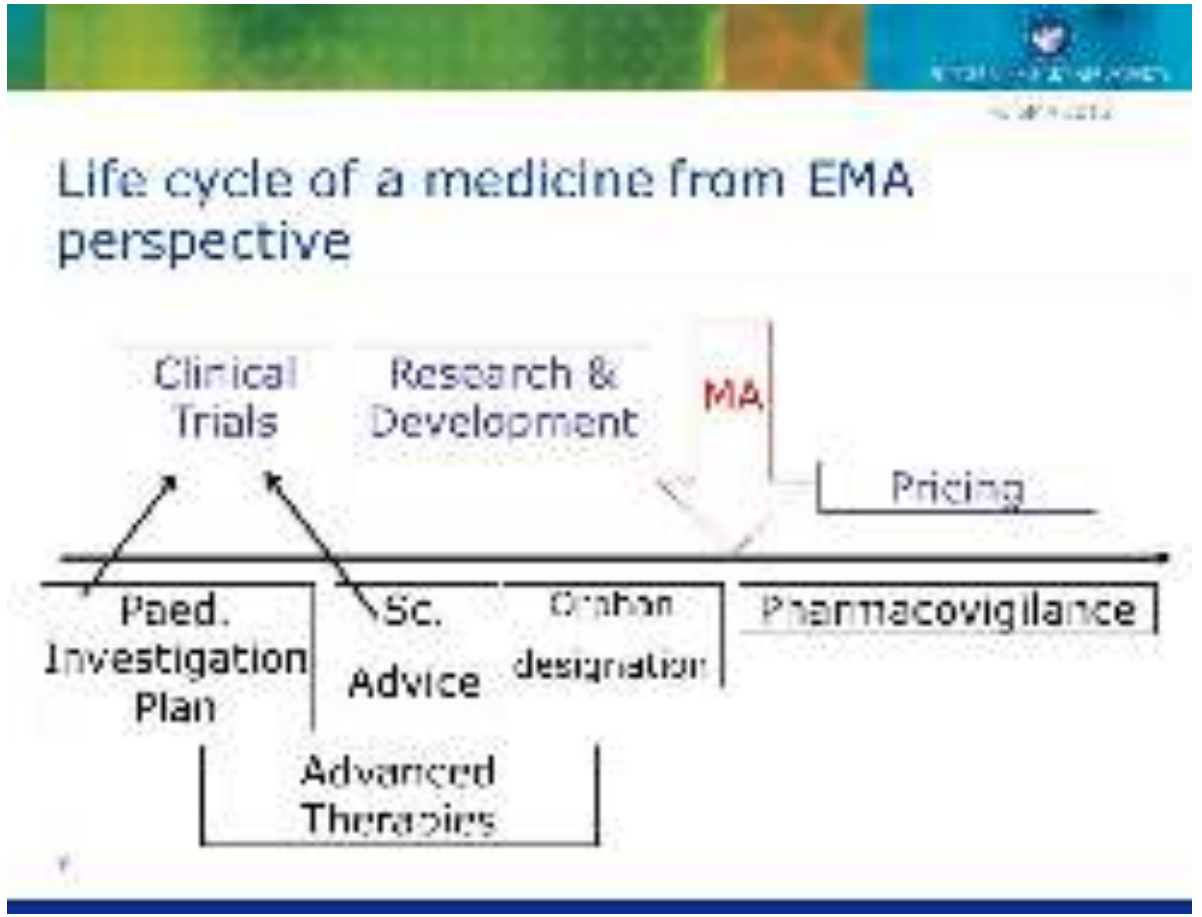
EMA REGULATORY PROCEDURE FOR CAR T-CELL THERAPIES

- Orphan designation
- Paediatric Investigation Plan/PIP compliance check
- MA: Centralised Authorisation Procedure
- PRAC/CHMP/CAT scientific evaluation
- COMP orphan designation maintenance
- EC market approval



EMA PIPELINE

MA Application

Submission date	Sponsor	Indication/Therapy
31 July 2017	Kite Pharma	Axicabtagene ciloleucel as a treatment for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL), and primary mediastinal B-cell lymphoma (PMBCL) who are ineligible for autologous stem cell transplant (ASCT)
6 November 2017	Novartis	CTL019 (tisagenlecleucel) application for the treatment of children and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant (ASCT)

MA Timeline

- ATMPs – ca. 120 days (if no delay)
- Kite granted access to Priority Medicines (PRIME) regulatory support for development and accelerated review of new therapies to treat patients with a high unmet need

CLINICAL DATA

Novartis, Kymriah®

Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (ALL) for patients aged from 3 to 25
n=63

- Phase II study,
- **82% of patients achieved complete remission**
- 48% experienced grade 3 or 4 cytokine release syndrome (CRS)

Relapsed/refractory diffuse large B-cell lymphoma (DLBCL), People > 18

- Phase II study, 81 infused patients
- At month 3, the complete remission rate was 32% and the PR rate 6%
- Among patients evaluable at 6 months, the CR rate was 30% and PR rate was 7%.
- CRS occurred in 58% of infused patients, with 15% grade 3 and 8% grade 4

CLINICAL DATA

Gilead/Kite, Yescarta®

Diffuse large B cell lymphoma (DLBCL) and other B Cell lymphomas

- 101 infused patients
- Complete response rate of 31% in 77 patients with DLBCL after 8.7 months of follow-up
- **51% of the patients, not just DLBCL, in complete remission**
- 13% of patients experienced grade 3 or CRS and 31 percent experienced neurologic toxicities

Juno, JCAR017

Diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) or transformed follicular lymphom

- **Complete response rate of 73% in 15 DLBCL patients at three month**

CAR T-CELL THERAPIES: PATIENT AND INVESTOR EXPECTATIONS

PATIENTS AND FAMILIES

- Hope for a cure
- Strong willingness to access

INVESTORS: A CAR T-CELL DEAL REVIEW

- 2012, 3 deals
- 2015, 35 deals
- Between 2012 and Septembre 2016, the deals worth at least:
  - $2 billion in disclosed upfront payments
  - $4 billion in milestones, royalties…
- August 2017, Gilead's Kite Pharma acquisition for $11,9 billion

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PRICING ISSUE

Highly personalised

+ Large health benefits

+ Difficult and supposedly expensive to produce

+ A response to an unmet medical need

+ Strong willingness to access

+ High investment return expectations

= **HIGH PRICES**

HOW MUCH?

UK PREDICTIONS

National Institute for Health and Care Excellence (NICE) ran the numbers and found that CAR T-cell therapies **could be worth up to $649.000**, assuming that patients gain 10 QALYs over the current standard of care - **NICE willing to pay up to $460,000** for this new technology

U.S. PRICES

THERAPY	ALL	DLBCL	
Kymriah®	$475,000 + 1 month outcome based contracting	?	Novartis CEO Jimenez sees an opportunity for indication based pricing, based on the value it brings to the healthcare system Might be two prices, one for ALL, a second for DLBCL
Yescarta®	XX	$373.000 without outcome based contracting	Gilead CEO Milligan finally said that they could be open to risk sharing agreements

A clear lack of transparency

THE PUBLIC SECTOR ROLE IN FUNDING CAR T TECHNOLOGIES

- David Mitchell, Patients for Affordable Drugs, calculated that NIH poured $200 million into research that led to CAR T Therapy
- Only 20% of CAR T-cell trials are sponsored by pharmaceutical industry (Hartmann et al. *EMBO-Molecular Medicine*, 2017)
- Jimenez, Novartis, says that bringing Kymriah® to market cost more than $1 billion
- KEI notes that Kite reported spending $317 million in R&D from 2012 to June 30, 2017, and is selling the company for $11.9 billion

CAR T MANUFACTURING COSTS AND LACK OF TRANSPARENCY

- 2017, the French Health minister, Agnes Buzyn, explained that CAR-T Cells were going to be expensive because of manufacturing costs. Is that so?
  - 2012, New York Times, Dr. June said that producing engineered T-cells costs about $20,000 per patient http://www.nytimes.com/2012/12/10/health/a-breakthrough-against-leukemia-using-altered-t-cells.html
  - 2015, Kite Chief Financial Officer Cynthia Butitta said that its financial models set a base case price at $150,000 per treatment
  - 2017, Novartis's cost of goods for Kymriah® is reportedly around $200,000 https://www.apmhealtheurope.com/freestory/10/54546/car-t-costs-should-fall-after-first-approval--though-lack-of-skilled-workforce-could-signal-future-problems

= CLEAR LACK OF TRANSPARENCY

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WHAT'S NEXT?

Yescarta® and Kymriah® = first in class

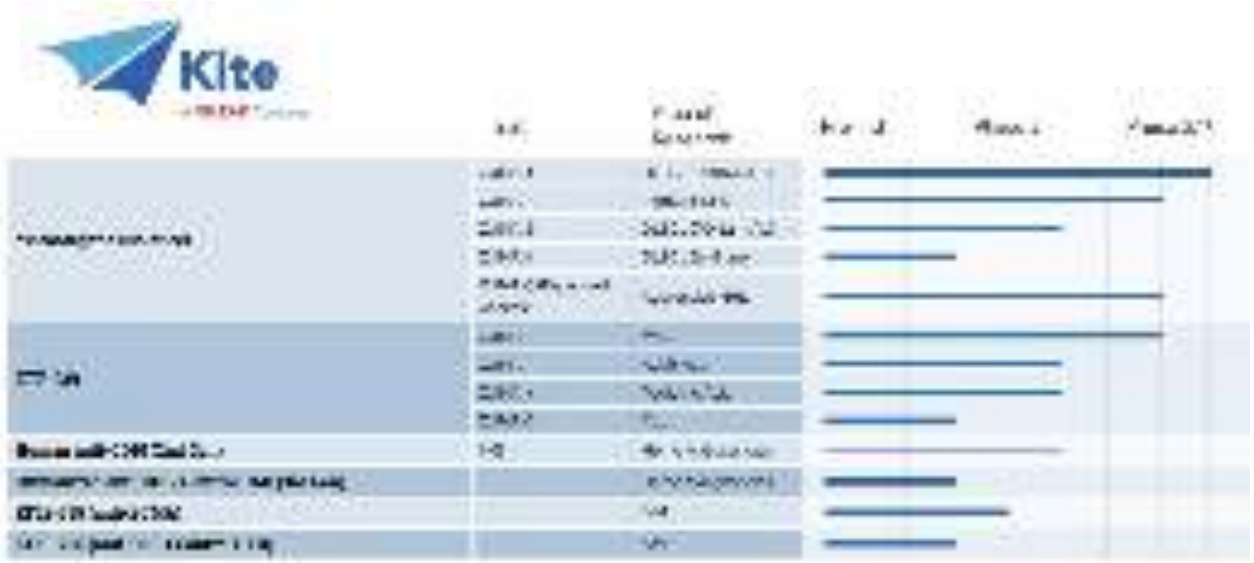
- Setting a benchmark
- Pricing critical

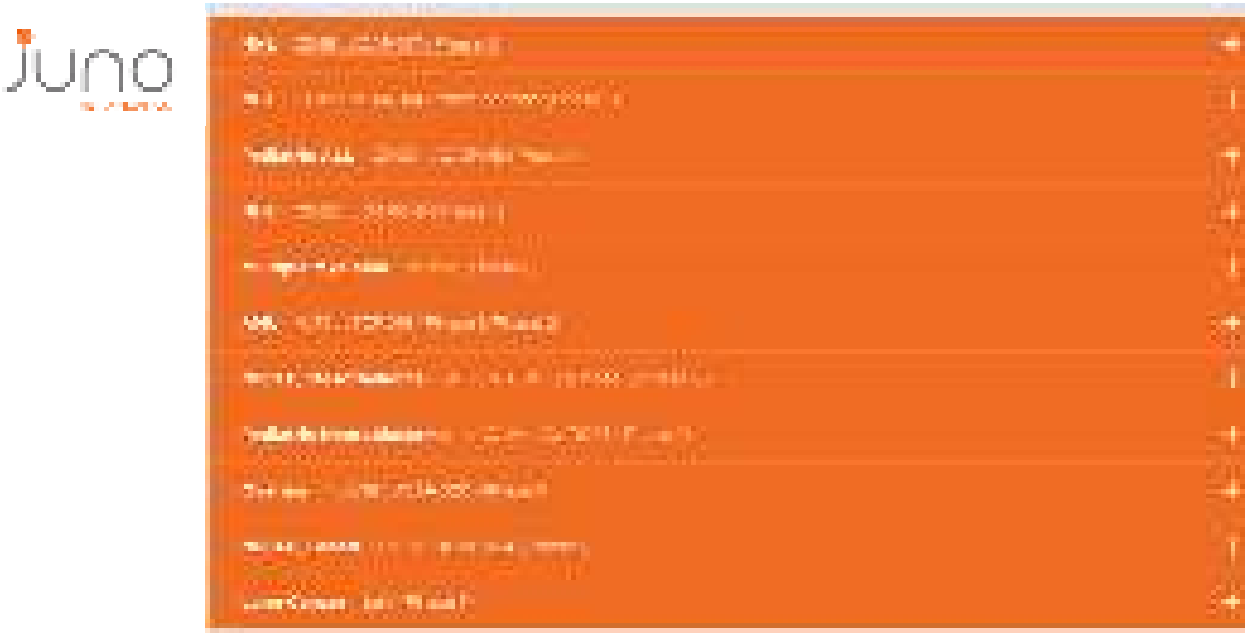
The most advanced CAR T targets hematological malignancies, rare cancers

- This space will soon be too crowded
- And it will become more and more important to target solid tumors

78 clinical trials on solid tumors (Diane Singhroy, September 15th, 2017, *Knowledge Ecology International* https://www.keionline.org/23419/)

- Lung, Breast, Ovarian, Multiple Myeloma etc.





CAR T-CELL THERAPIES

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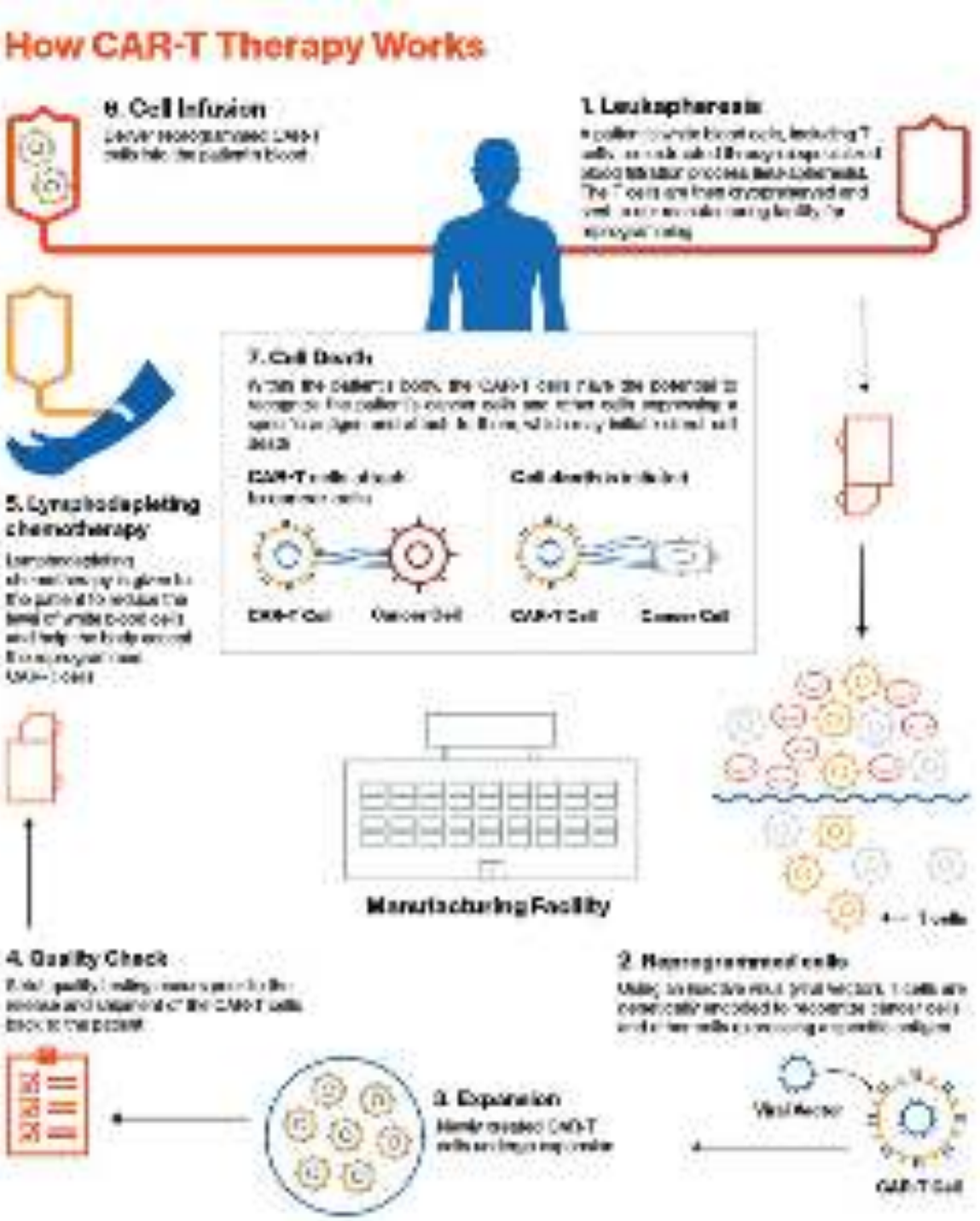
THANK YOU FOR YOUR ATTENTION!