FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

DIENST HEMATOLOGIE UZ GENT

IMMUNOTHERAPIE MET T-CELLEN: VAN STAMCELTRANSPLANTATIE TOT CAR-T CELLEN: ONZE PAARDEN VAN TROJE IN DE STRIJD TEGEN KANKER

LOTUZ SYMPOSIUM- 30 NOVEMBER 2019

Prof. Dr. Tessa Kerre

UNIVERSITEIT GENT

UZ GENT

CRIG CANCER RESEARCH INSTITUTE GHENT

ION immuno-oncology network Ghent

fwo

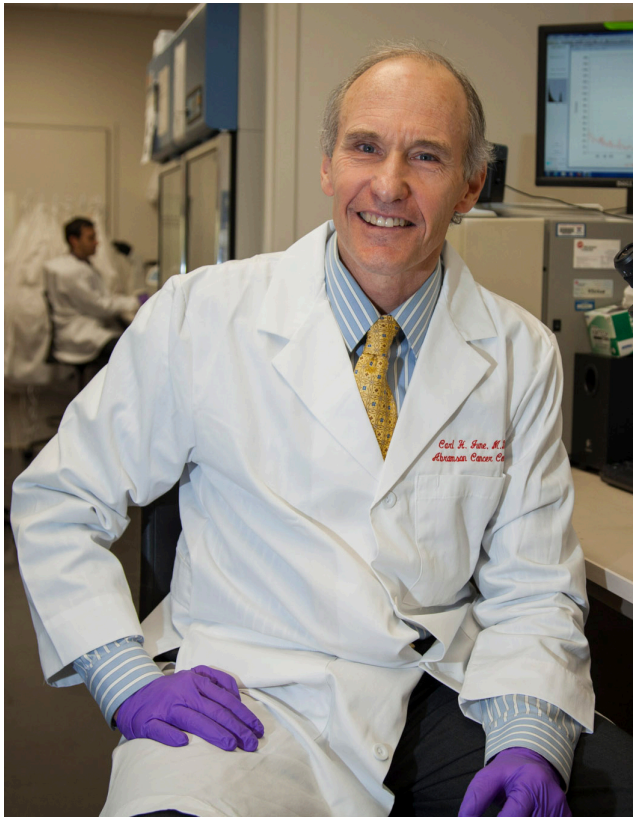
HET VERHAAL VAN EMILY

UNIVERSITEIT GENT

HET VERHAAL VAN EMILY

UNIVERSITEIT
GENT

HET VERHAAL VAN EMILY



Carl June

UNIVERSITEIT GENT

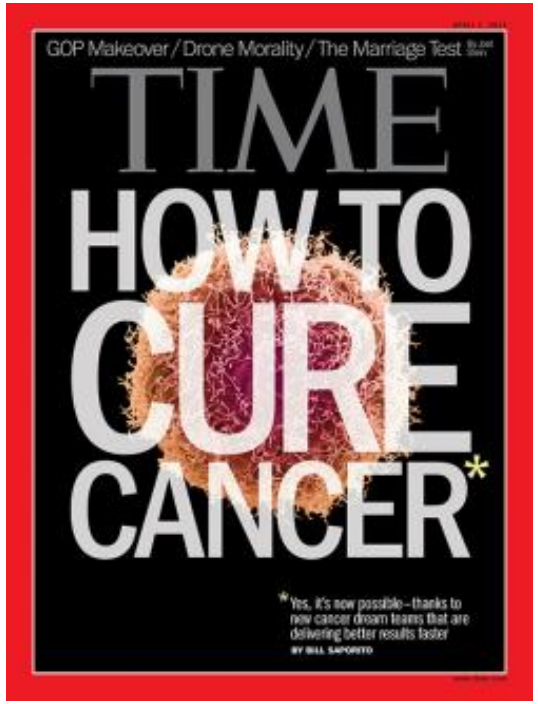
HET VERHAAL VAN EMILY

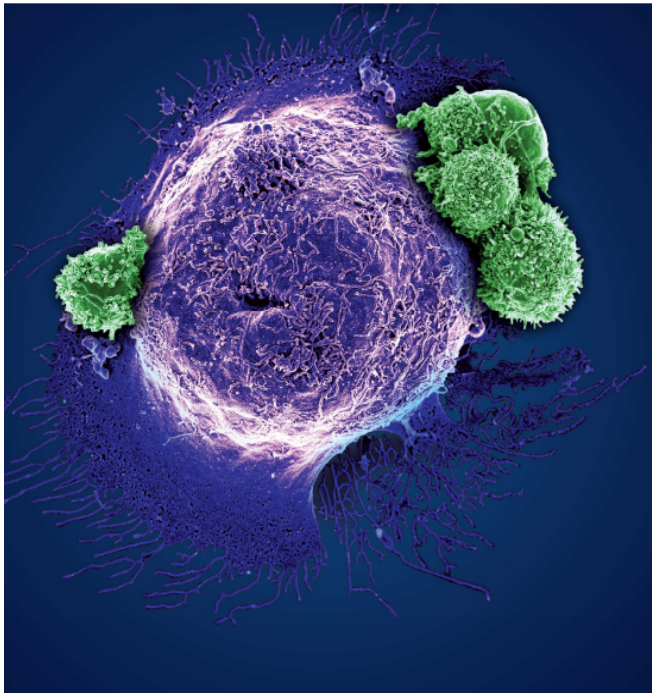
Emily Whitehead

© The Emily Whitehead Foundation

UNIVERSITEIT GENT

IMMUNOTHERAPIE

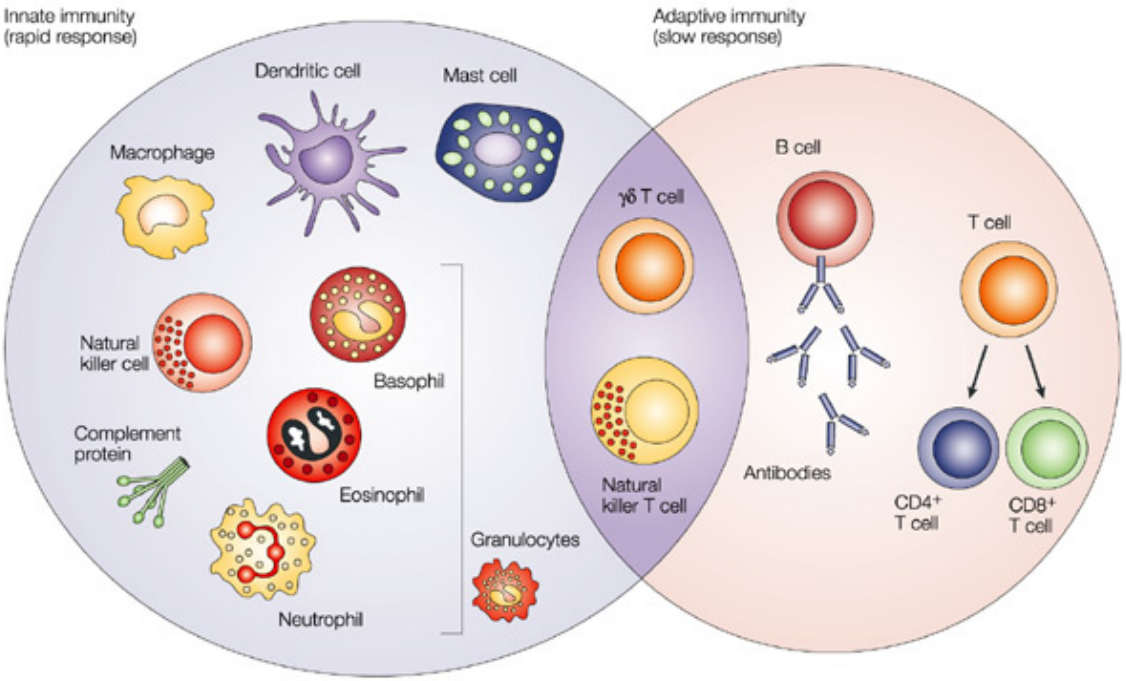




HET IMMUUNSYSTEEM EN KANKER

UNIVERSITEIT GENT

HET IMMUUNSYSTEEM



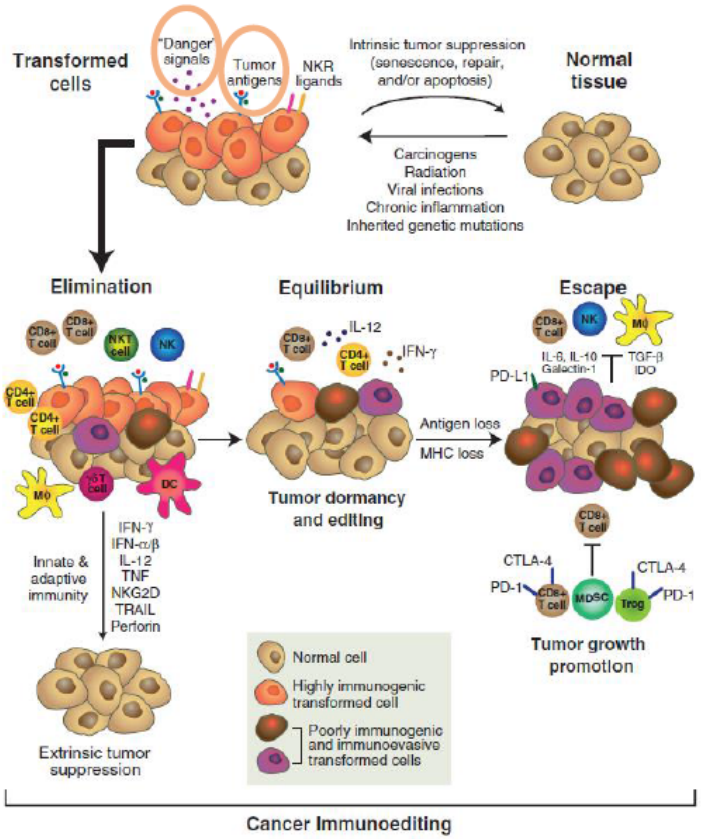
Nature Reviews | Cancer

UNIVERSITEIT
GENT

Dranoff G. Nature Reviews Cancer, 2004

HET IMMUUNSYSTEEM EN KANKER

– Interacties immuunsysteem en kanker

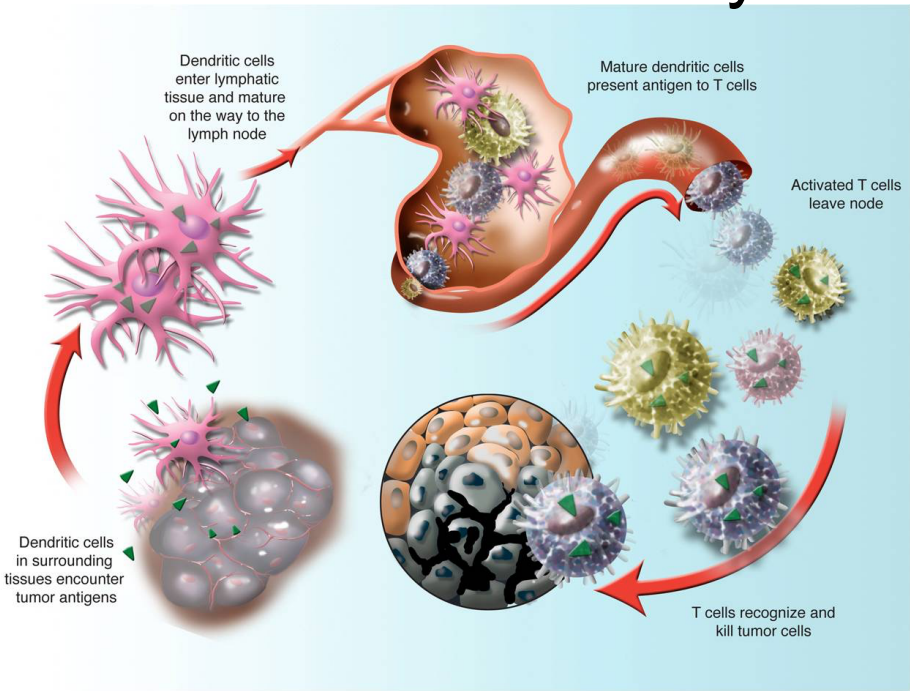


UNIVERSITEIT GENT

Hanahan and Weinberg, Cell 2000
Schreiber et al, Science 2011

HET IMMUUNSYSTEEM EN KANKER

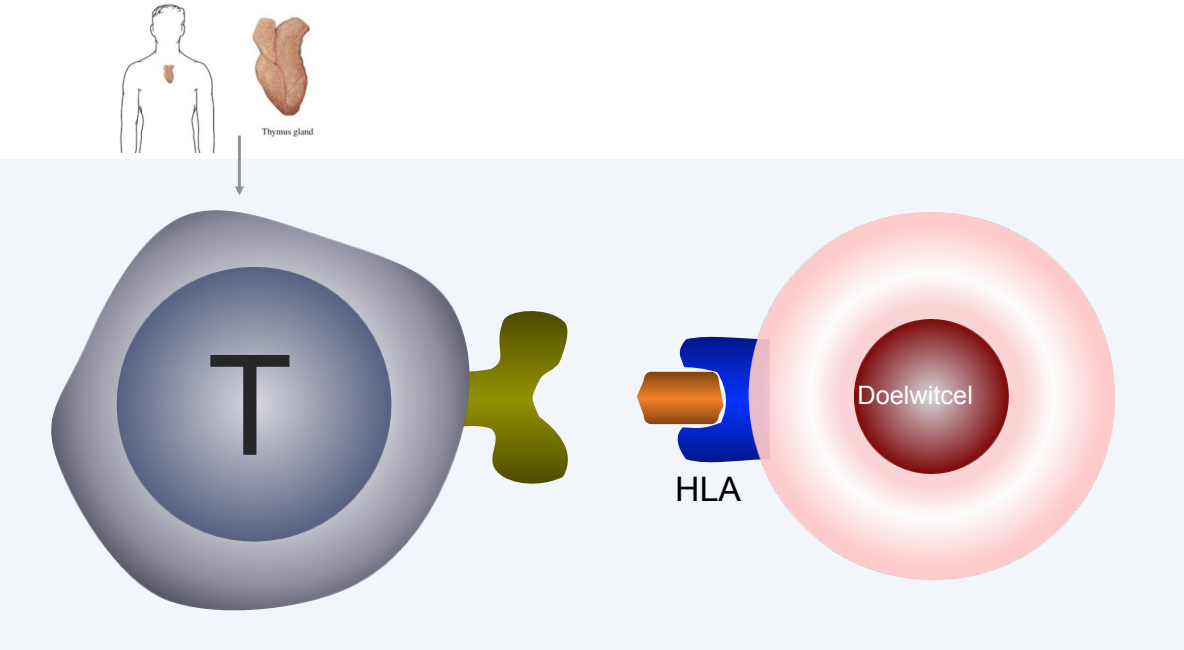
– Interacties immuunsysteem en kanker



UNIVERSITEIT GENT

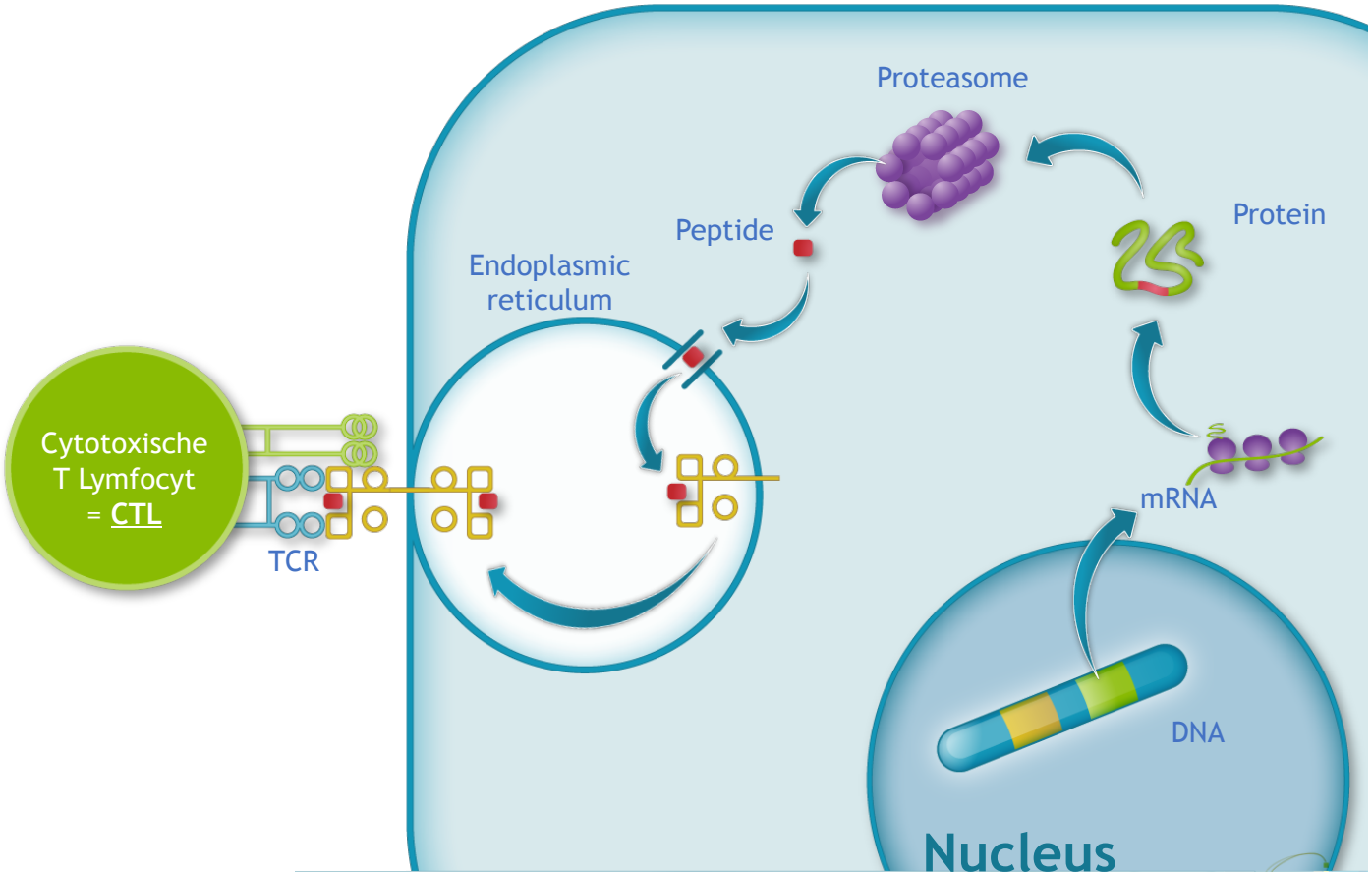
HET IMMUUNSYSTEEM EN KANKER

– T cellen herkennen doelwitcel



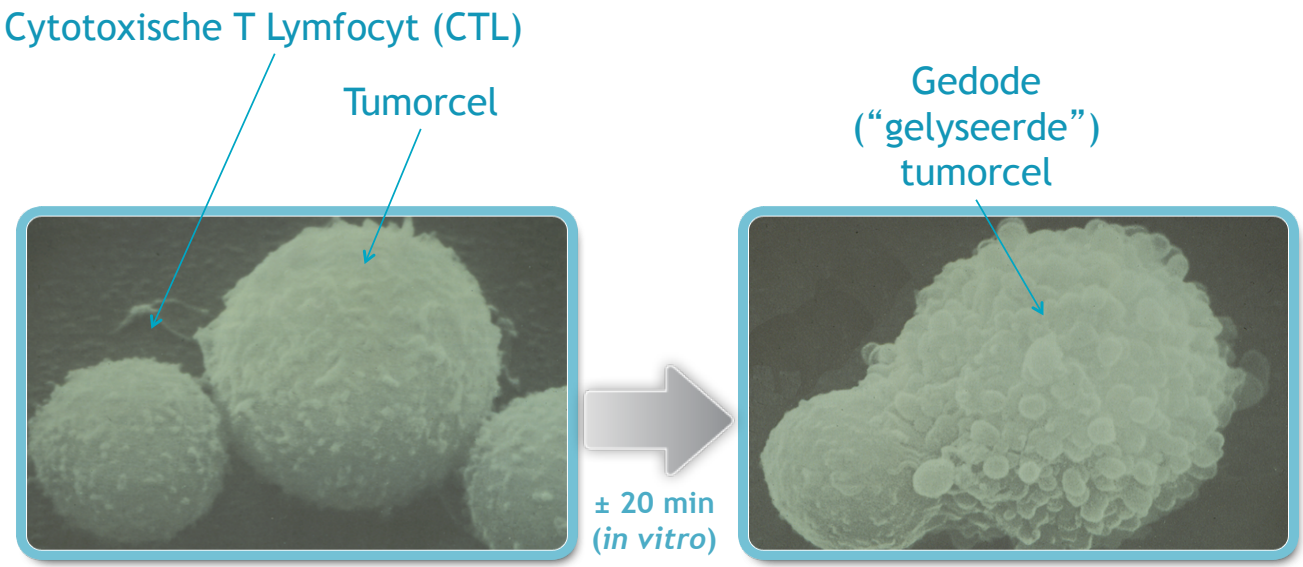
UNIVERSITEIT GENT

HERKENNING VAN DE TUMORCEL



UNIVERSITEIT
GENT

HET IMMUUNSYSTEEM EN KANKER



UNIVERSITEIT
GENT

WAAROM ONTSNAPT KANKER AAN HET MMUUNSYSTEEM?

- **Falend immuunsysteem**
  - T cellen die tumor herkennen zijn afwezig
  - T cellen die tumor herkennen worden onderdukt door:
    - immuunsuppressiva nemen
    - aids
    - chemotherapie/radiotherapie, …

- **Tumor ontsnapt actief aan het immuunsysteem**
  - Tumor vermomt zich als gezeonde cel (tumorantigenen en/of HLA molekules verdwijnen)
  - Aantrekken van cellen en oplosbare factoren, die afweerreacties onderdrukken
  - Expressie van eiwitten die binden op T-cellen, en daardoor de T-cellen onderdrukken

HOE KUNNEN WE HET IMMUUNSYSTEEM STERKER MAKEN IN DE STRIJD TEGEN KANKER?

→ IMMUNOTHERAPIE

UNIVERSITEIT GENT

OVERZICHT: IMMUNOTHERAPIE

- Actieve immunotherapie
  - Vaccinatie
    - Tumorextract
    - Peptide of mengsels van peptiden
    - Peptide gebonden op dendritische cellen
  - Modulatoire immunotherapie: checkpoint inhibitoren
- Passieve immunotherapie
  - Monoklonale antistoffen
  - Allogene stamceltransplantatie
  - T cel therapie
    - TCR/CAR transductie van circulerende T cellen
    - Antigen specifieke T cellen maken uit stamcellen

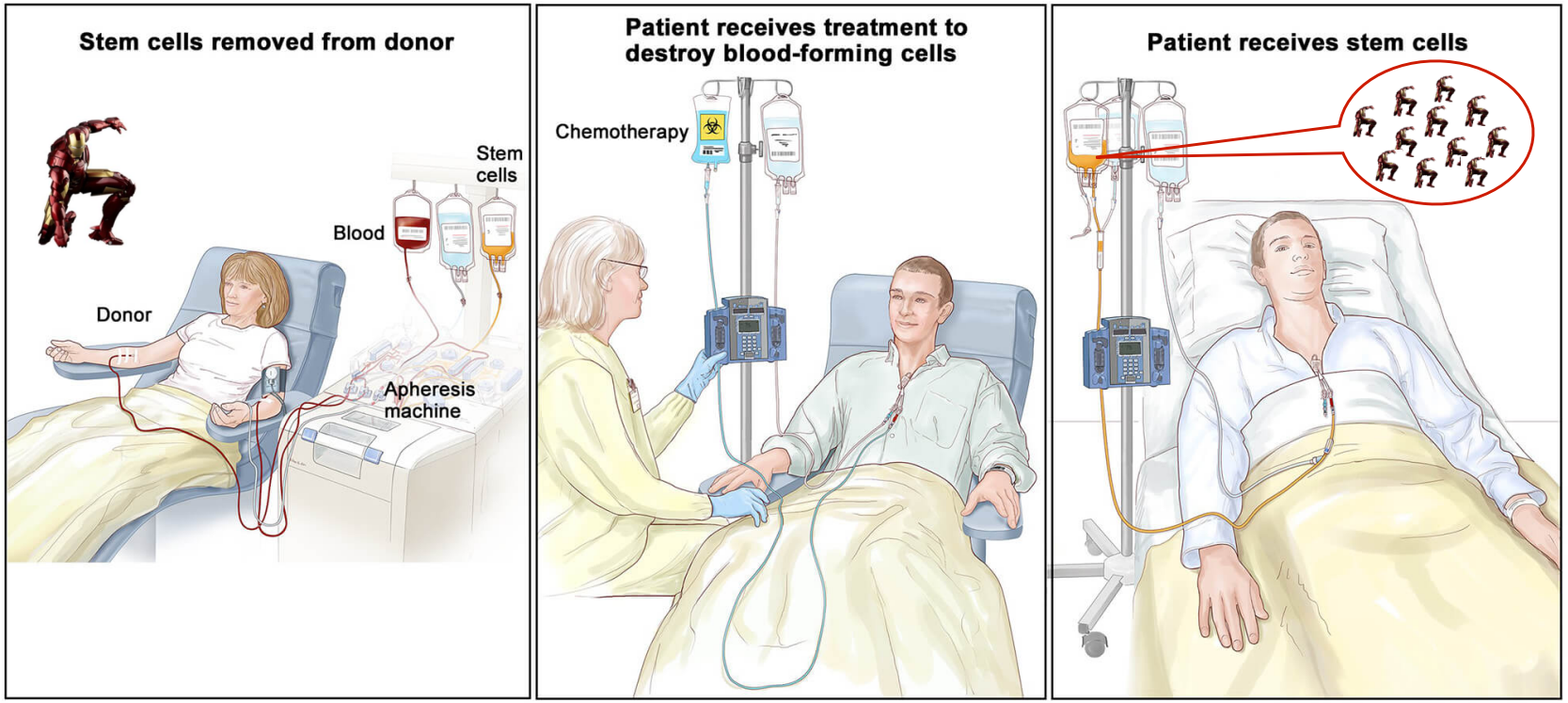
OVERZICHT: IMMUNOTHERAPIE

- Actieve immunotherapie
  - Vaccinatie
    - Tumorextract
    - Peptide of mengsels van peptiden
    - Peptide gebonden op dendritische cellen
  - Modulatoire immunotherapie: checkpoint inhibitoren
- Passieve immunotherapie
  - Monoklonale antistoffen
  - **Allogene stamceltransplantatie**
  - **T cel therapie**
    - TCR/CAR transductie van circulerende T cellen
    - Antigen specifieke T cellen maken uit stamcellen

ALLOGENE STAMCELTRANSPLANTATIE

UNIVERSITEIT GENT

ALLOGENE STAMCELTRANSPLANTATIE

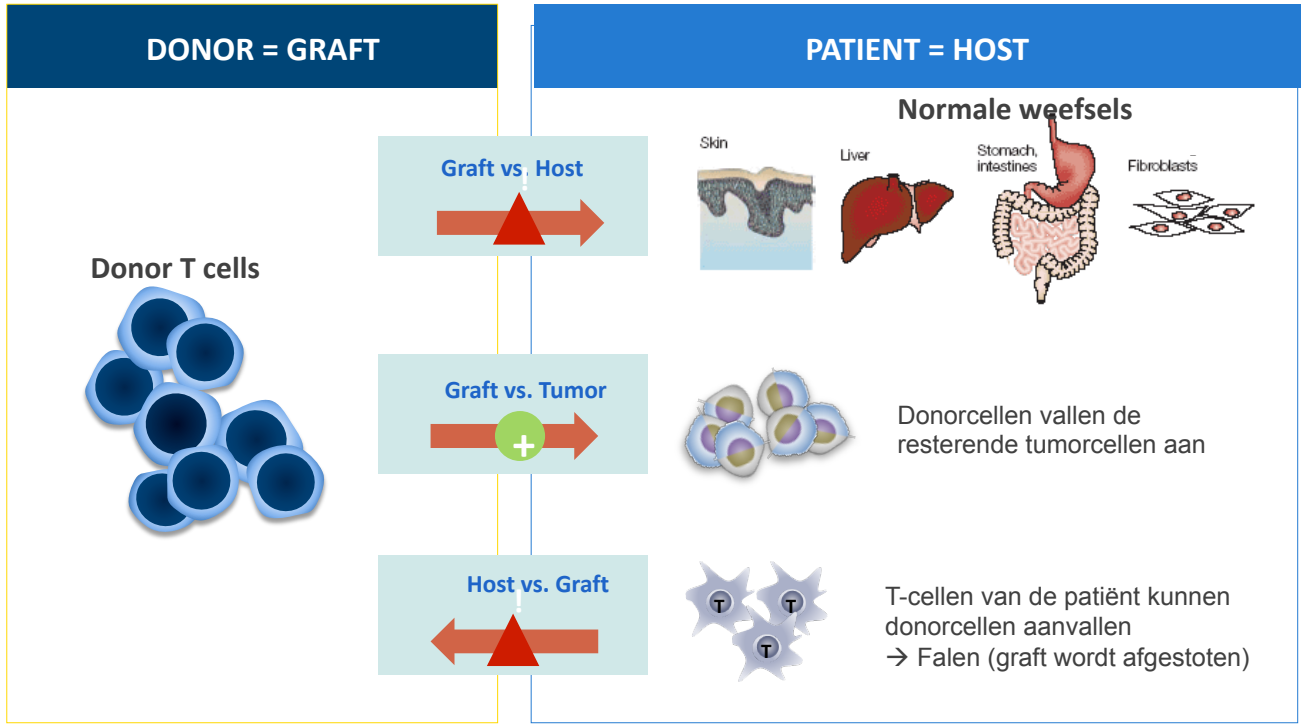


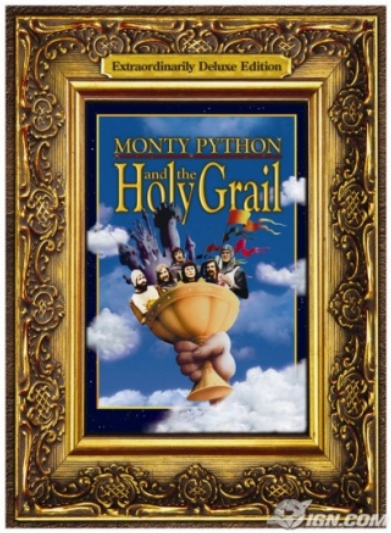
© 2011 Terese Winslow LLC
U.S. Govt. has certain rights

UNIVERSITEIT GENT

ALLOGENE STAMCELTRANSPLANTATIE

– Graft vs Host en Host vs Graft reacties





UNIVERSITEIT GENT

ALLOGENE STAMCELTRANSPLANTATIE

– Graft vs Host en Host vs Graft reacties

UNIVERSITEIT
GENT

ALLOGENE STAMCELTRANSPLANTATIE

UNIVERSITEIT
GENT

ALLOGENE STAMCELTRANSPLANTATIE

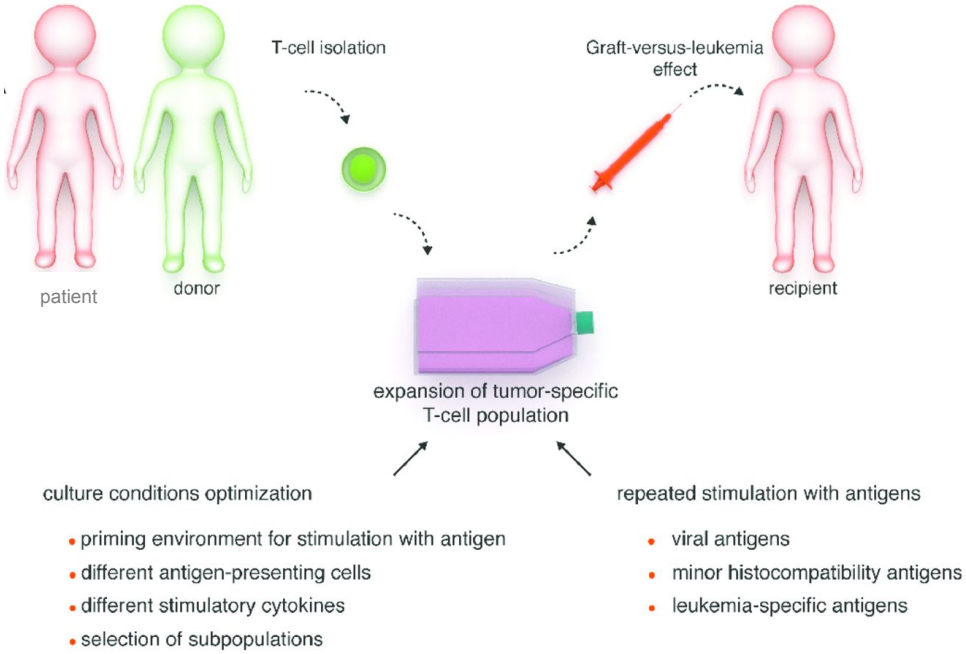
UNIVERSITEIT GENT

T-CEL THERAPIE

UNIVERSITEIT
GENT

T-CEL THERAPIE

– TIL/PBL



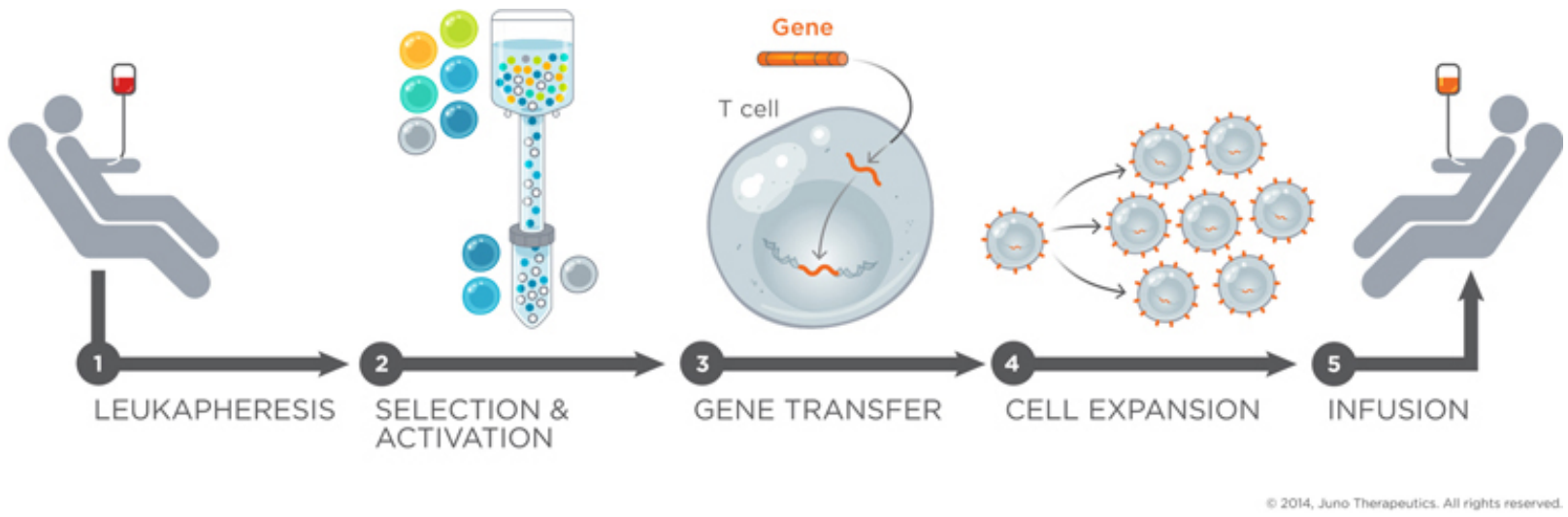
UNIVERSITEIT GENT

C. Russell Cruz, and Catherine M. Bollard Haematologica 2015

haematologica the hematology journal

T-CEL THERAPIE

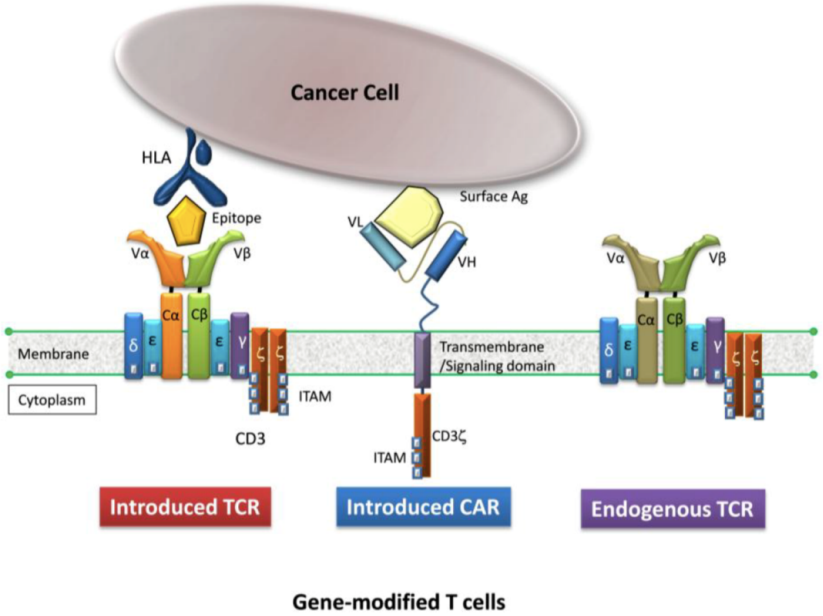
– Genetisch gemodificeerde T-cellen



UNIVERSITEIT GENT

T-CEL THERAPIE

– CAR/TCR



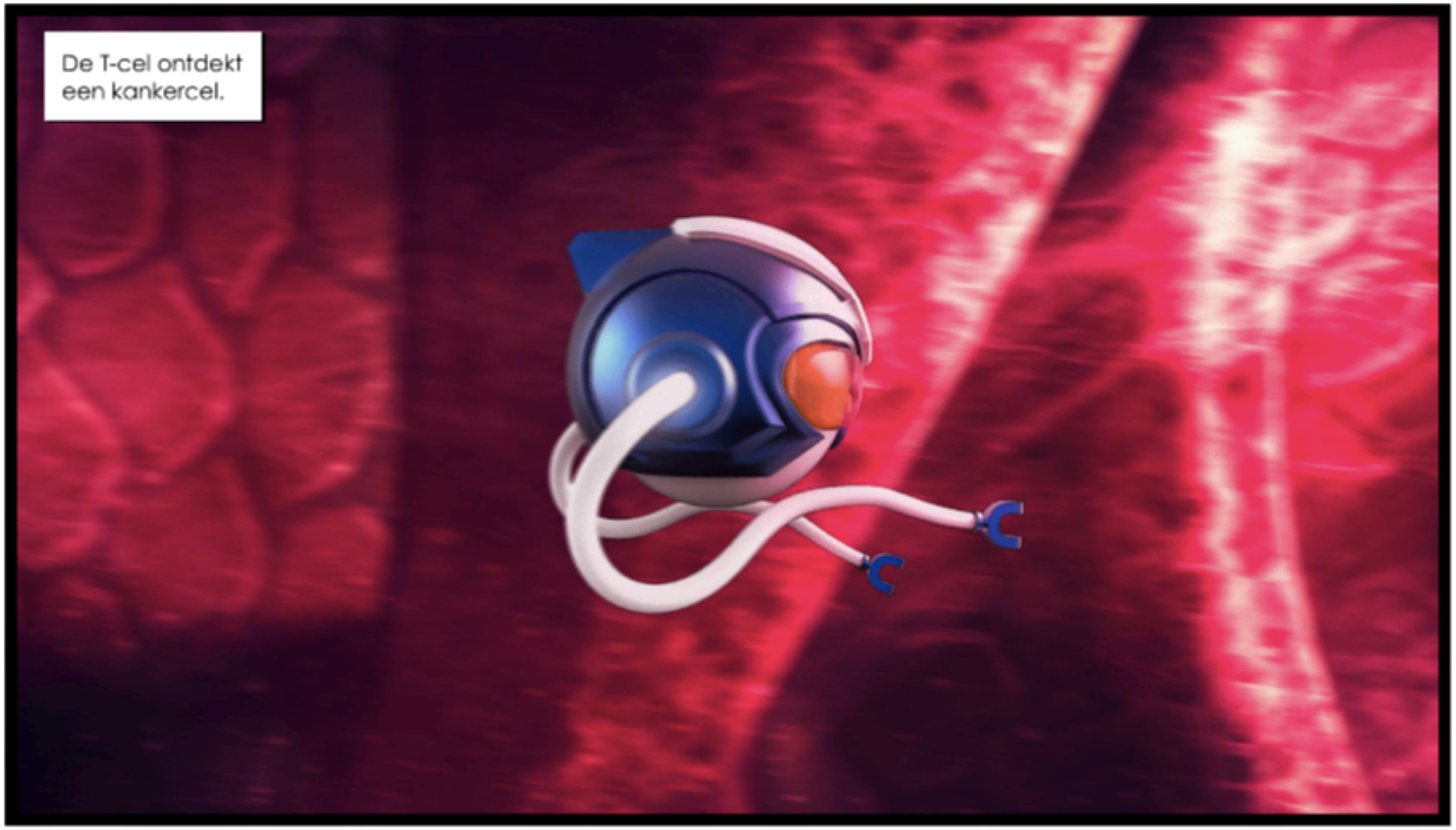
Gene-modified T cells

UNIVERSITEIT GENT

Hiroshi Fujiwara, Pharmaceuticals, 2014

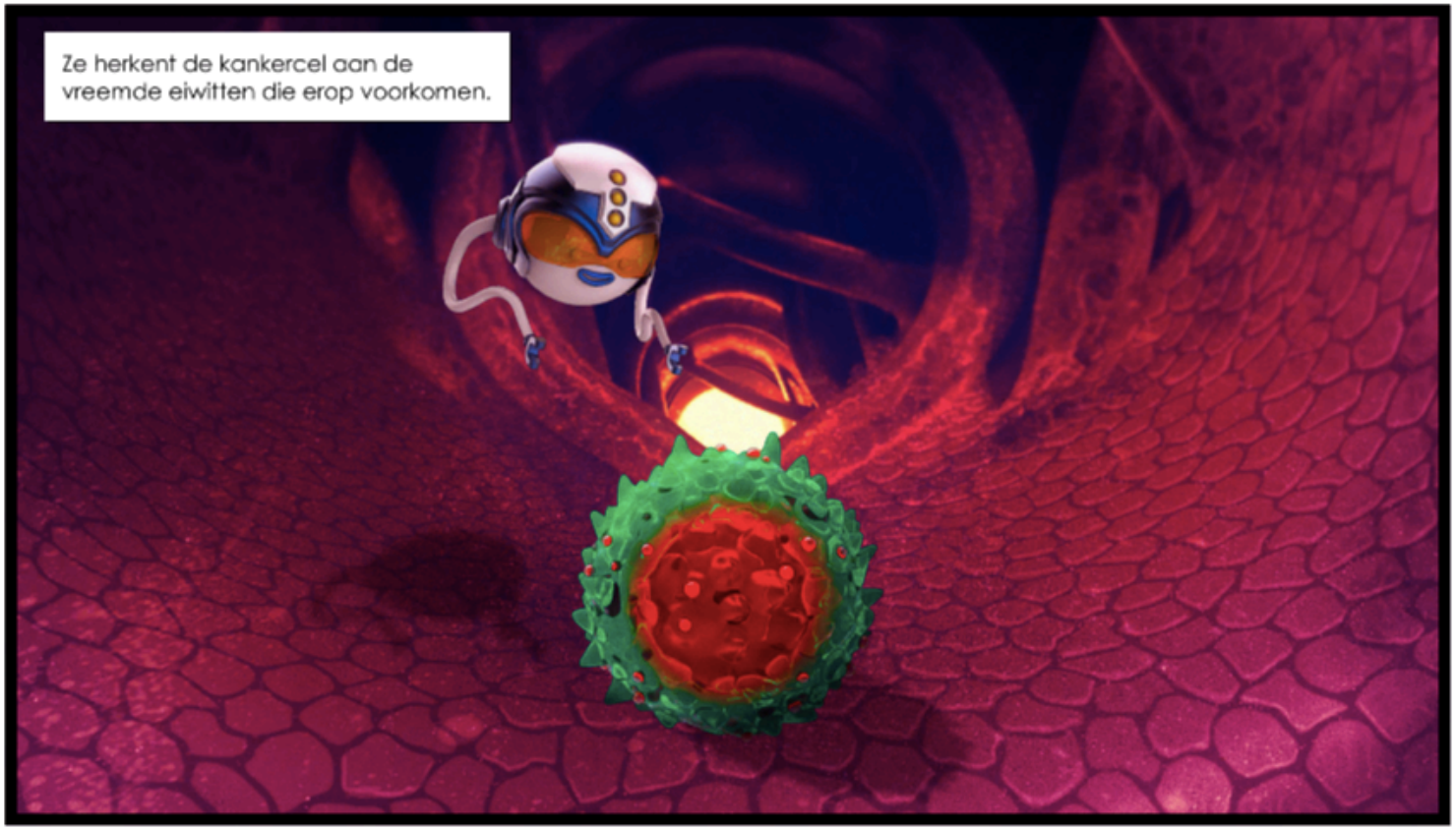
unity WebGL

immuno_web



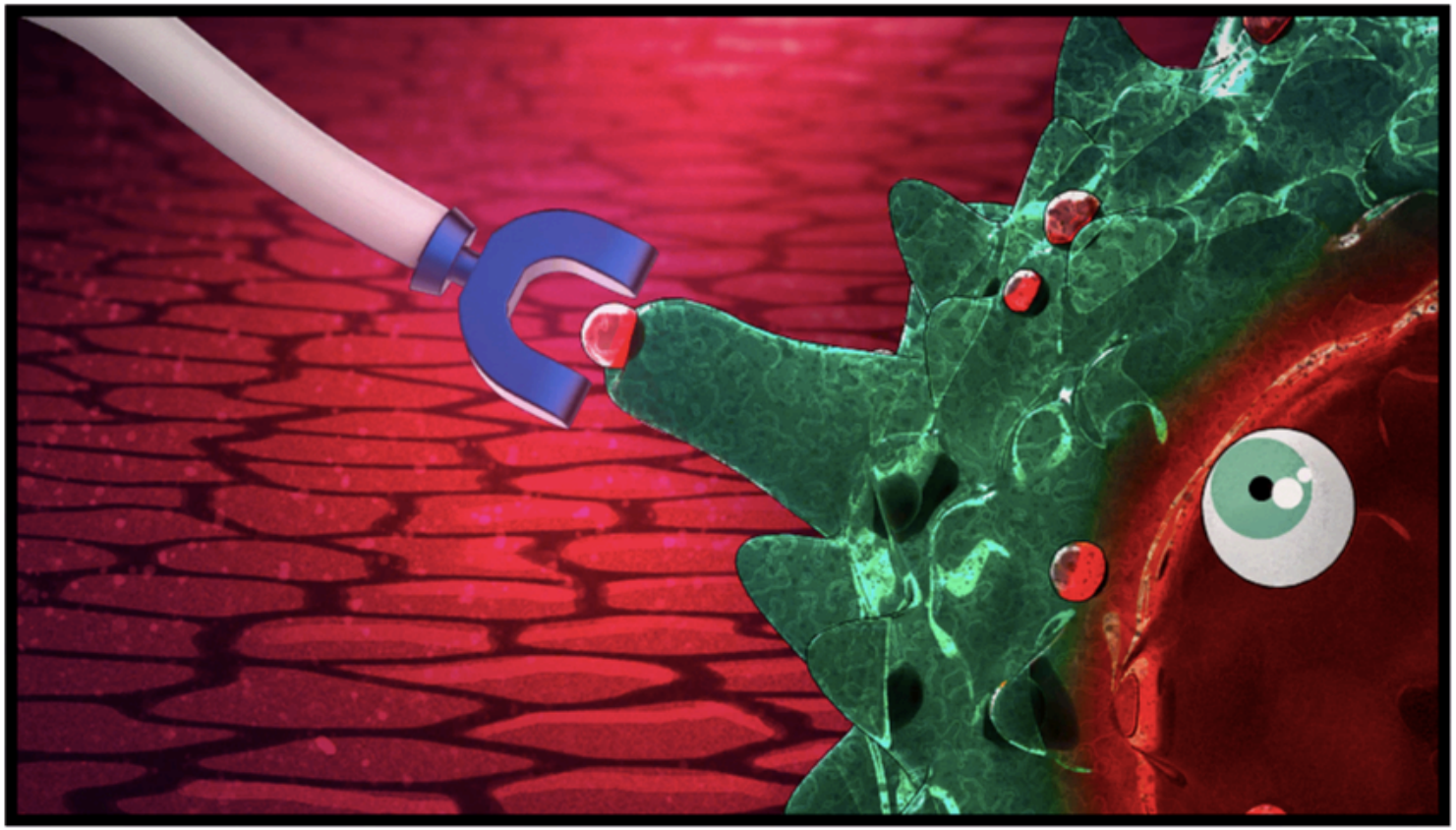
unity WebGL

immuno_web



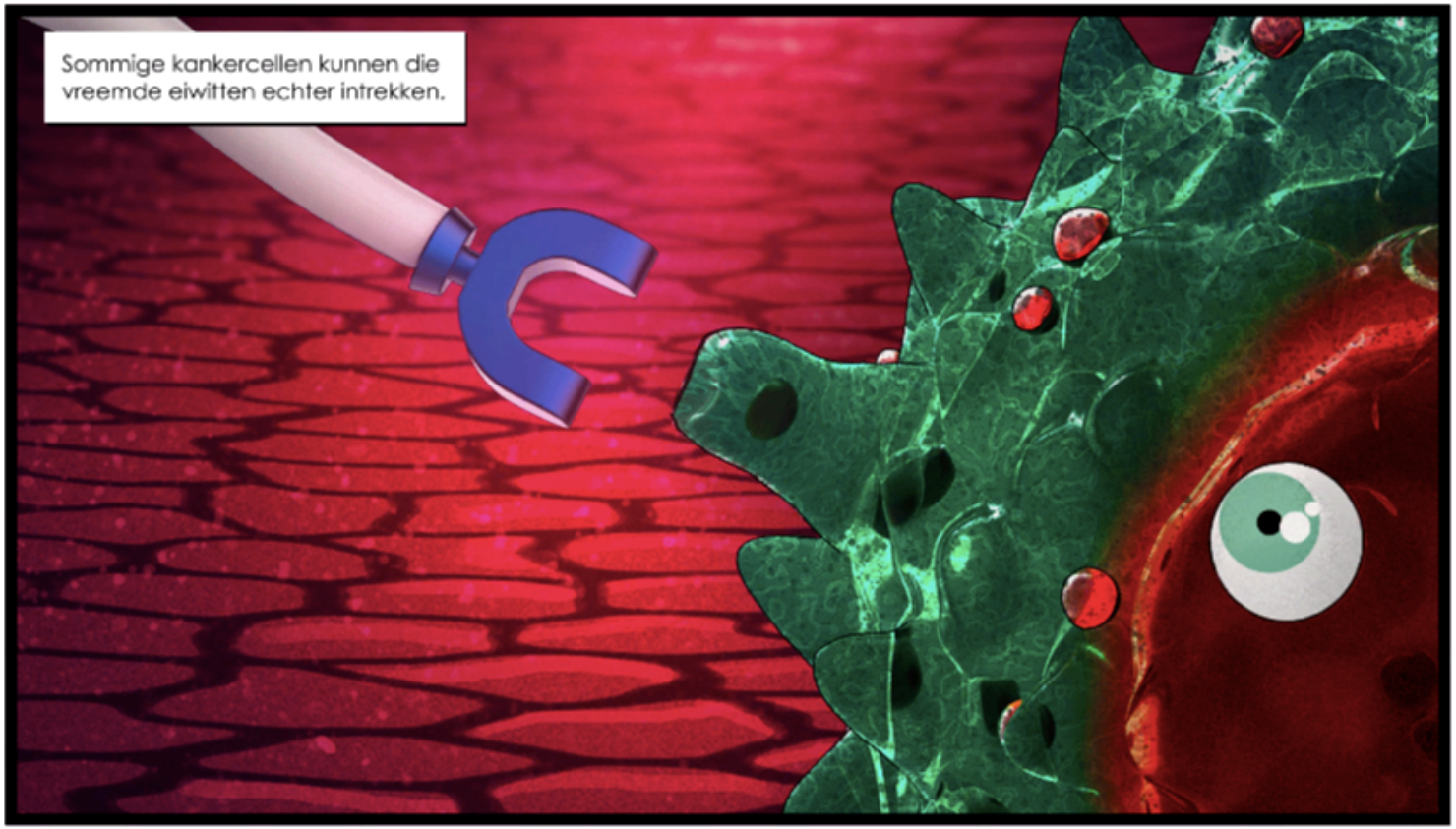
unity WebGL

immuno_web



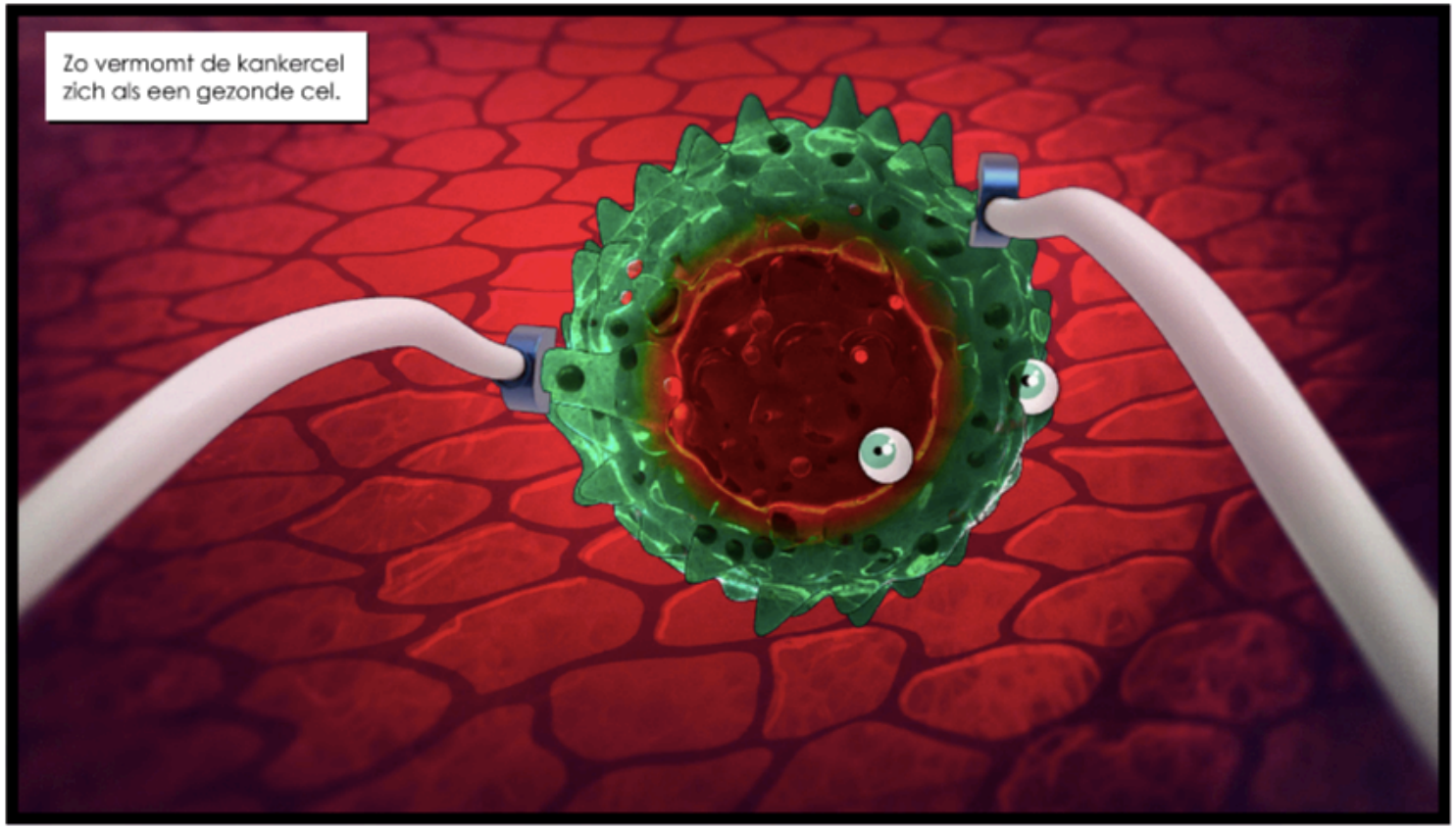
unity WebGL

immuno_web



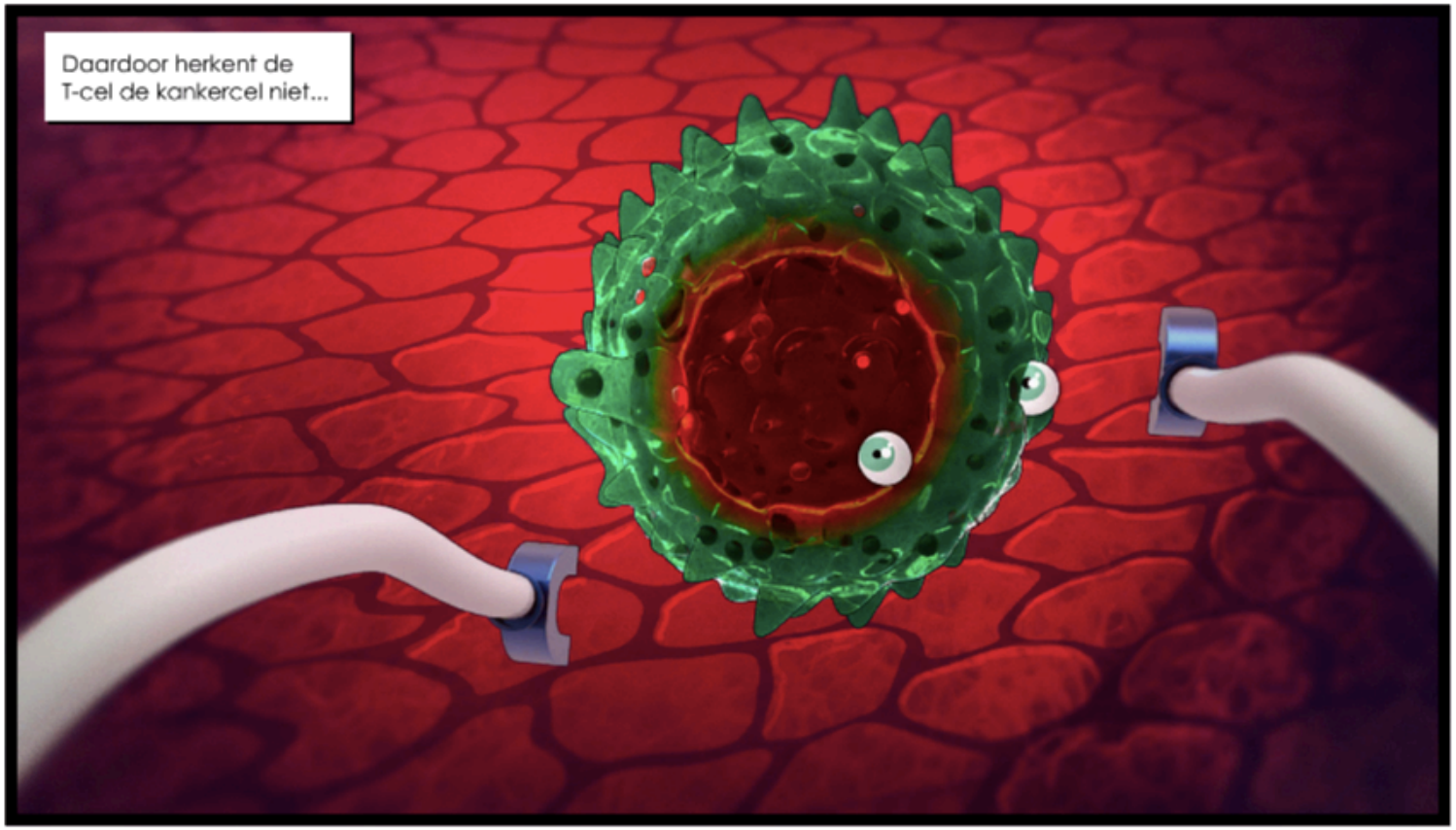
unity WebGL

immuno_web



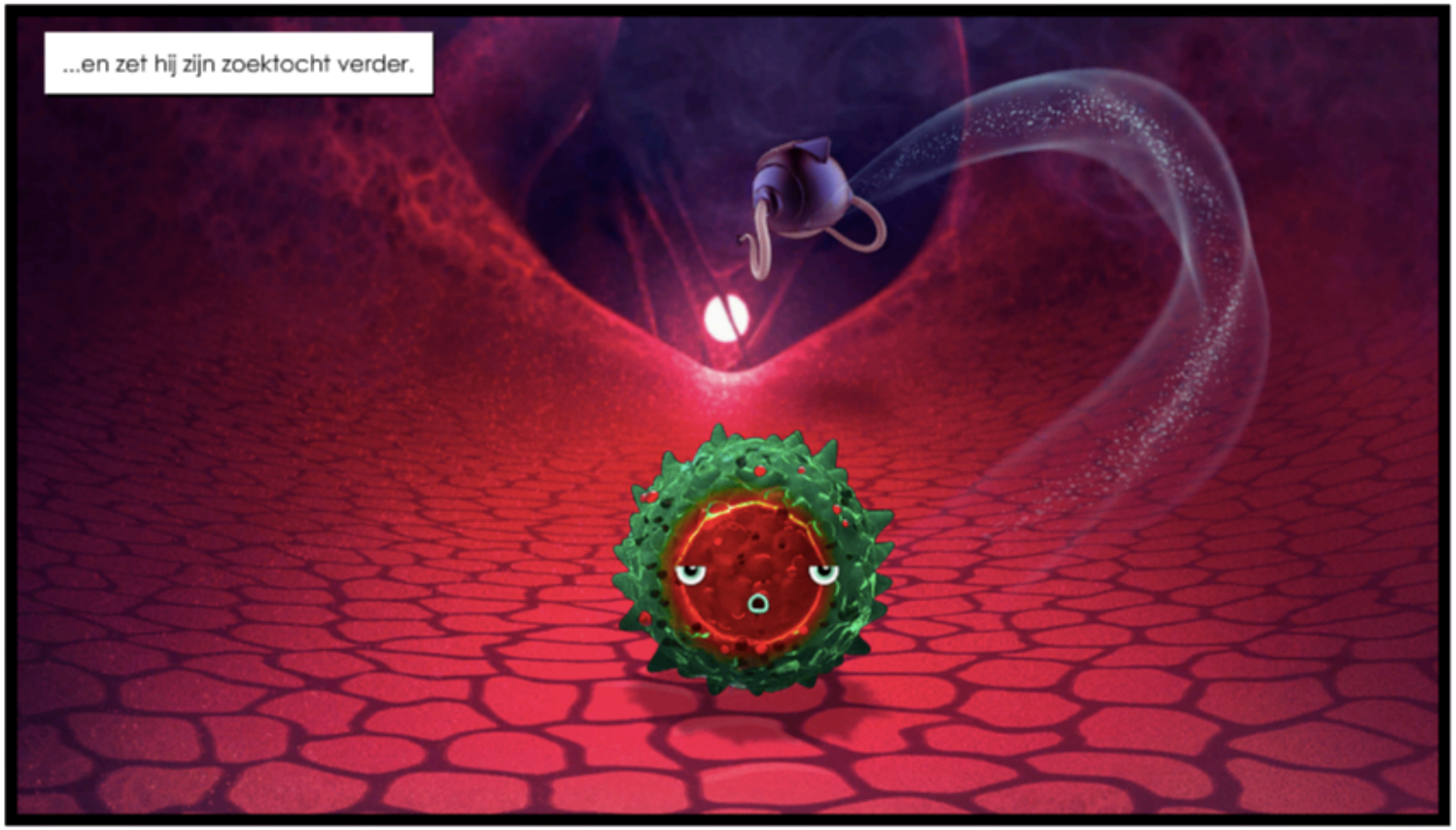
unity WebGL

immuno_web



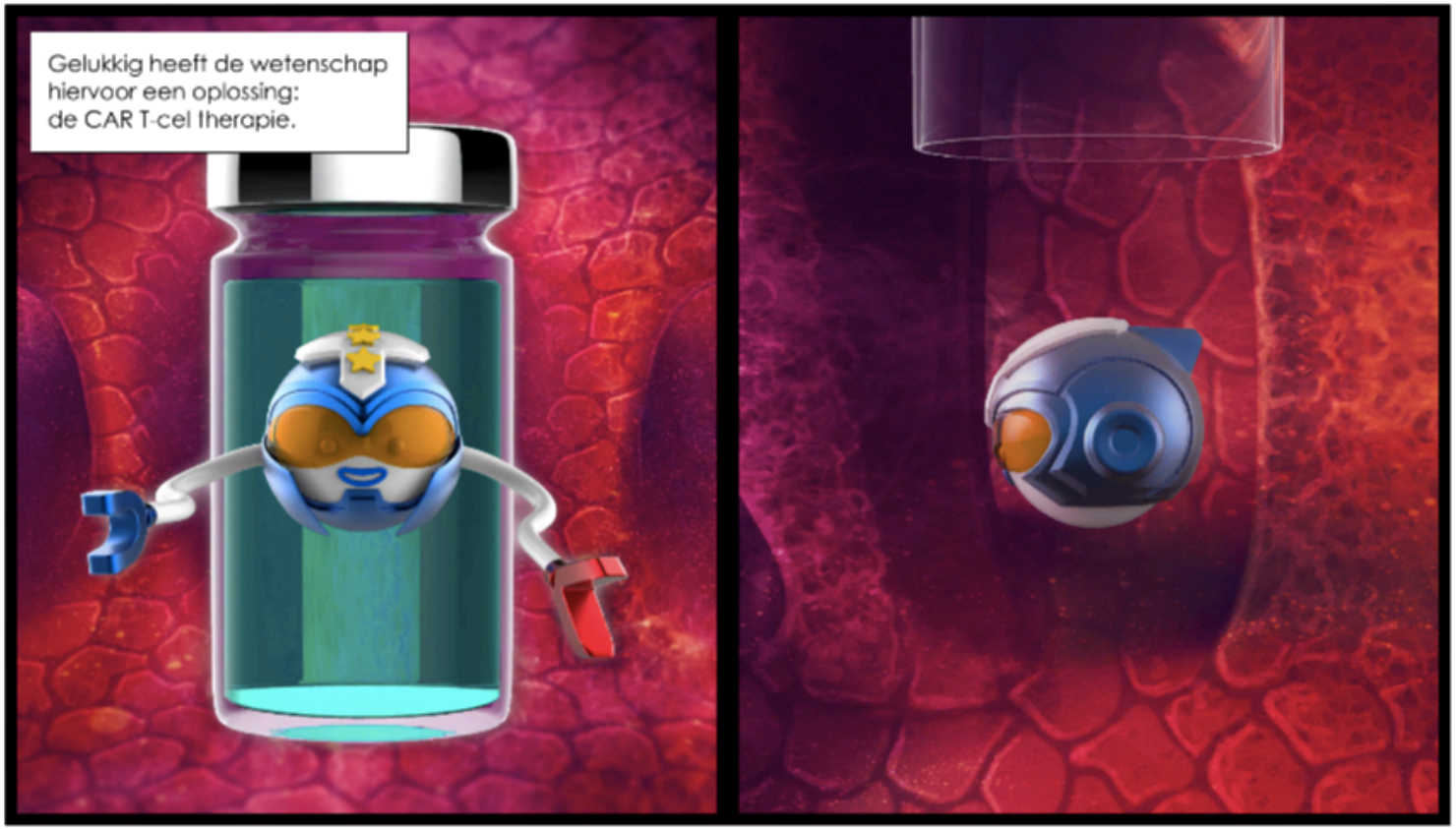
unity WebGL

immuno_web



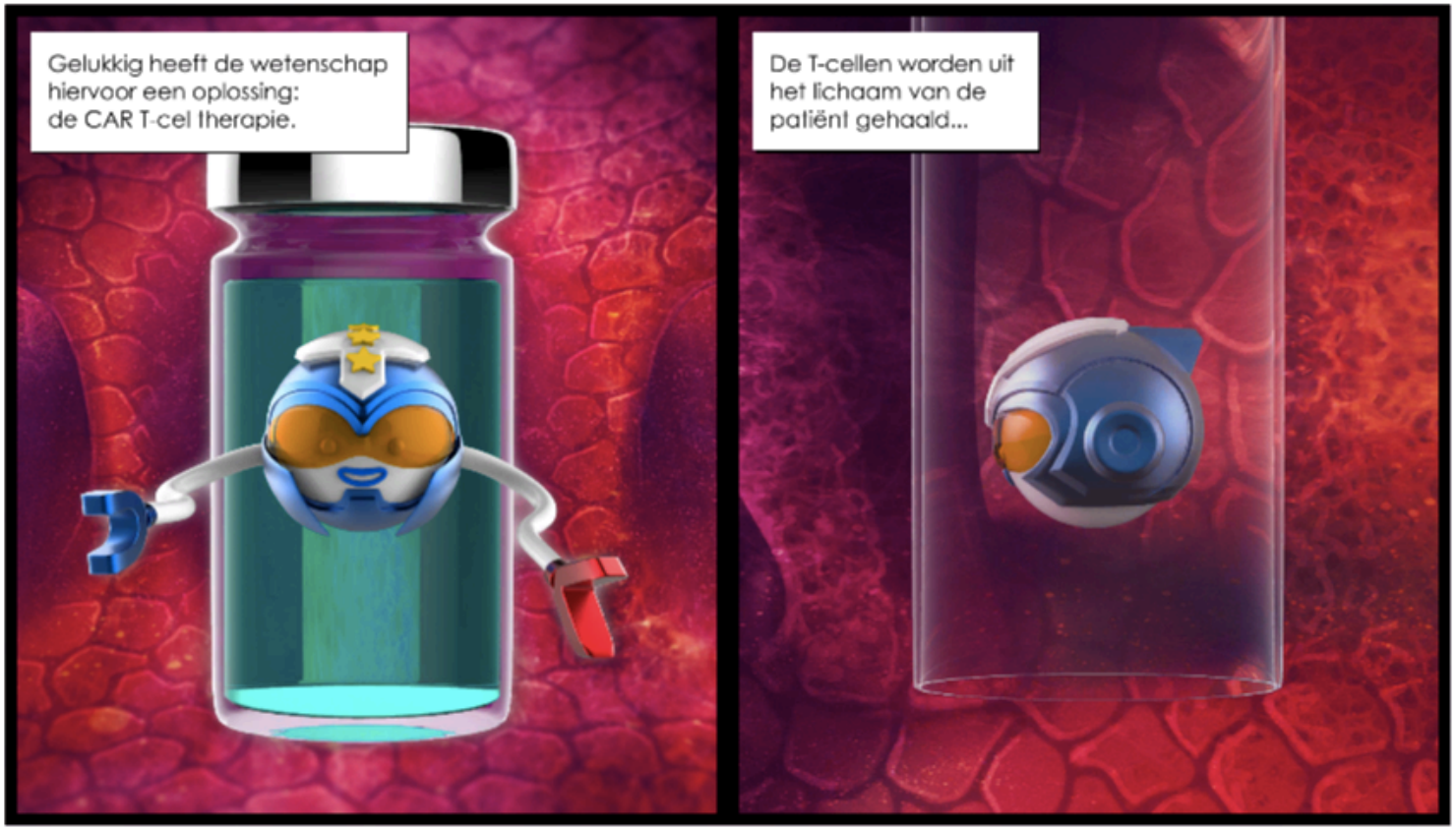
unity WebGL

immuno_web



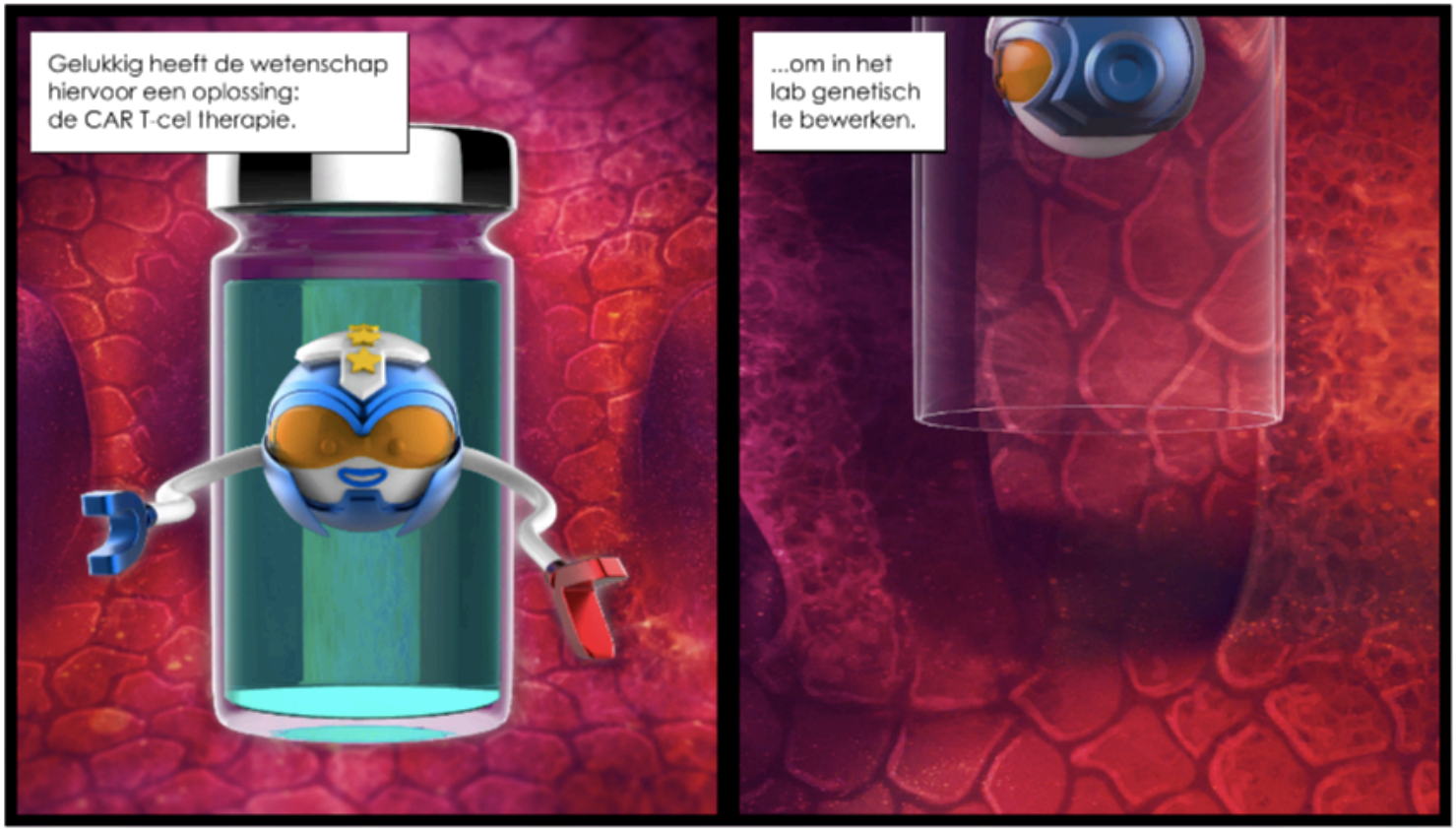
unity WebGL

immuno_web



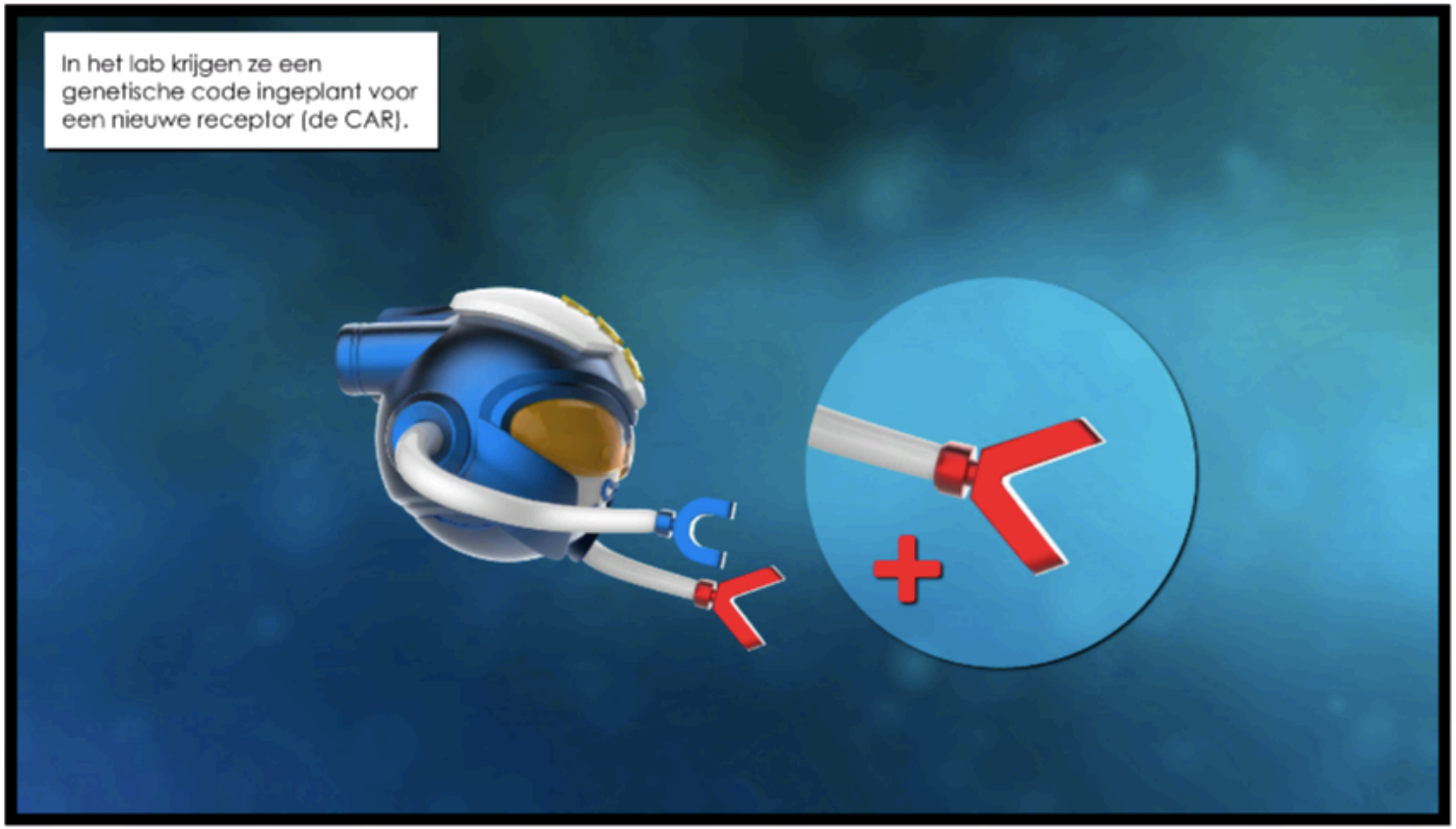
unity WebGL

immuno_web



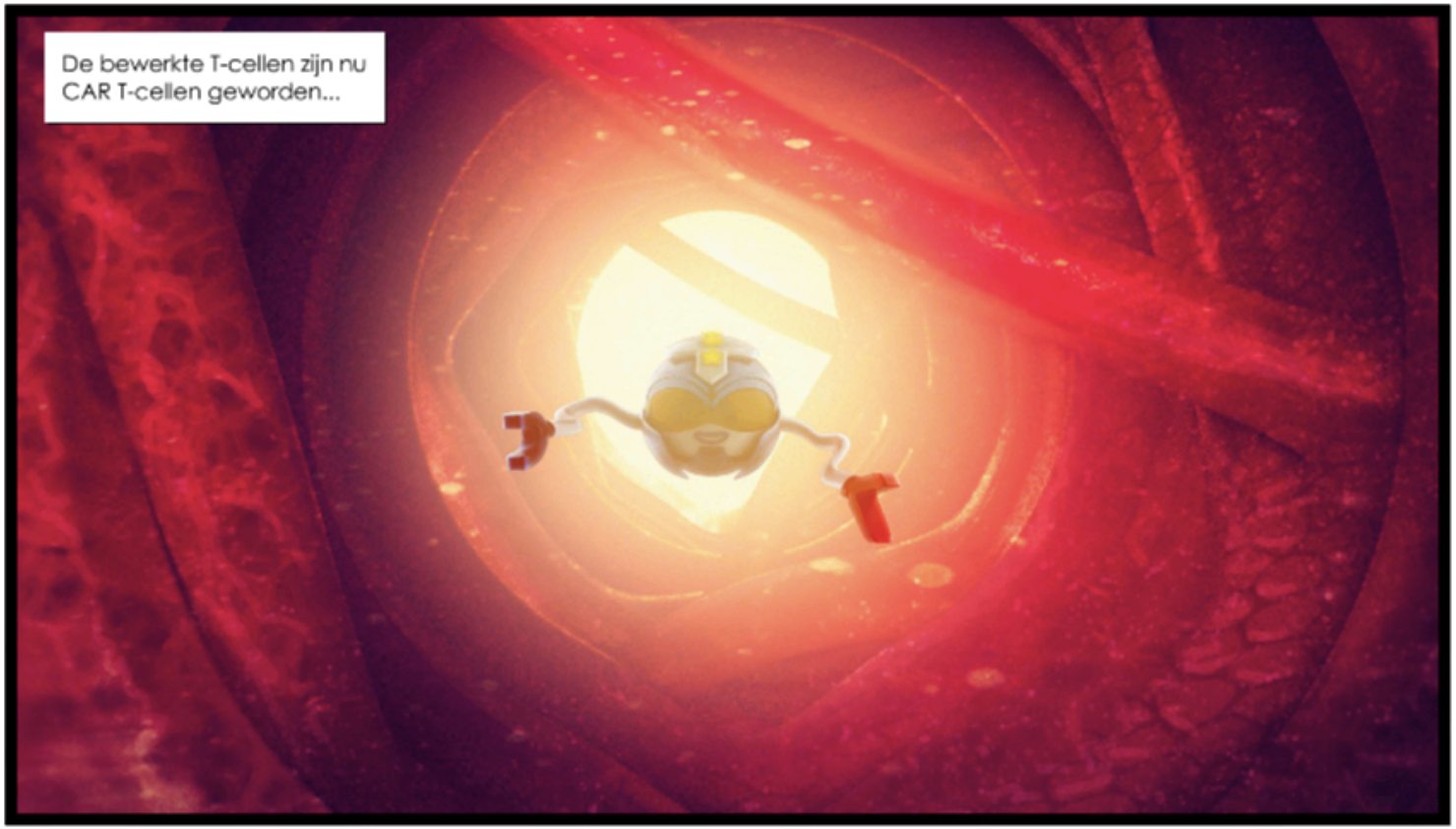
unity WebGL

immuno_web



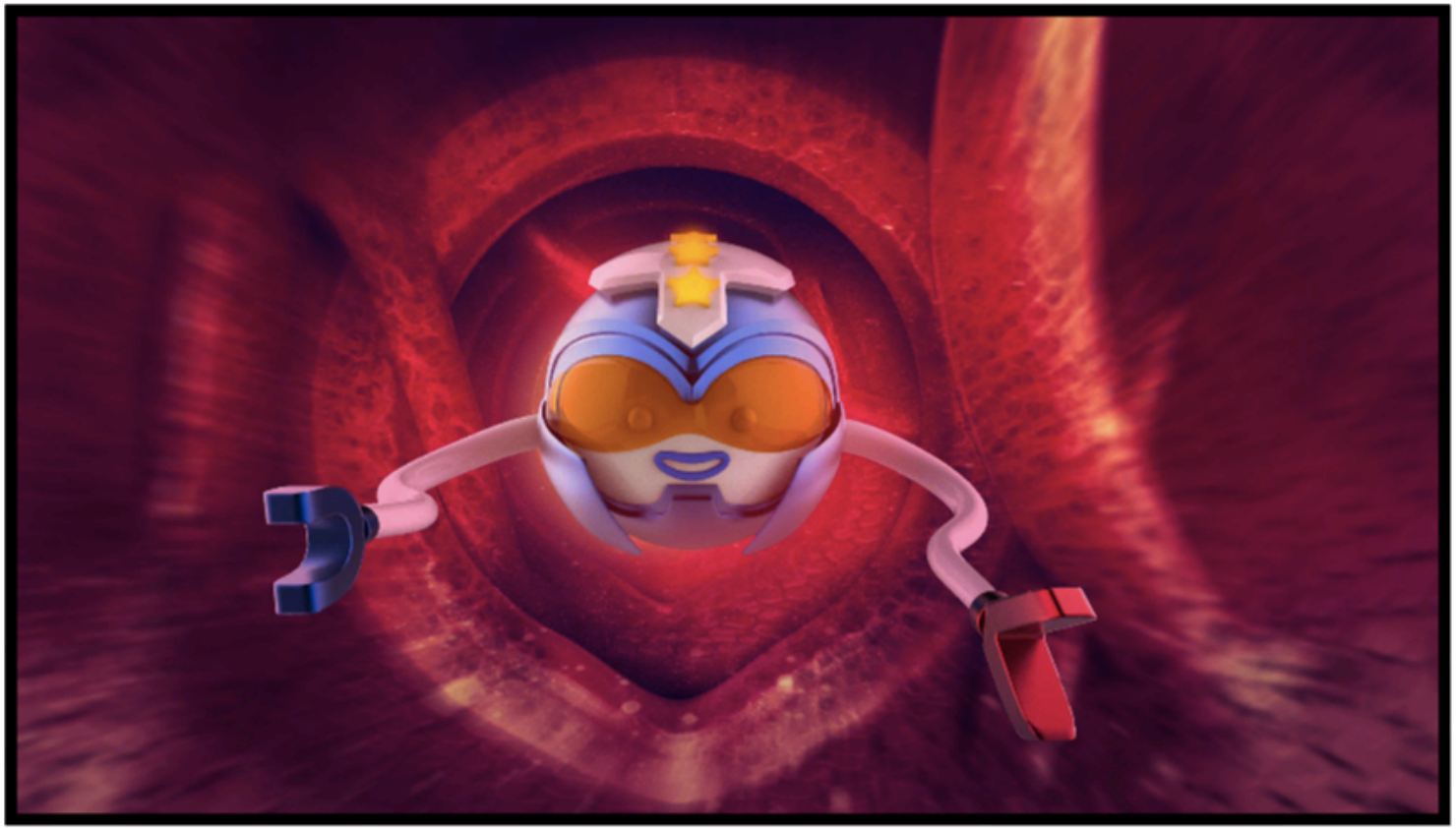
unity WebGL

immuno_web



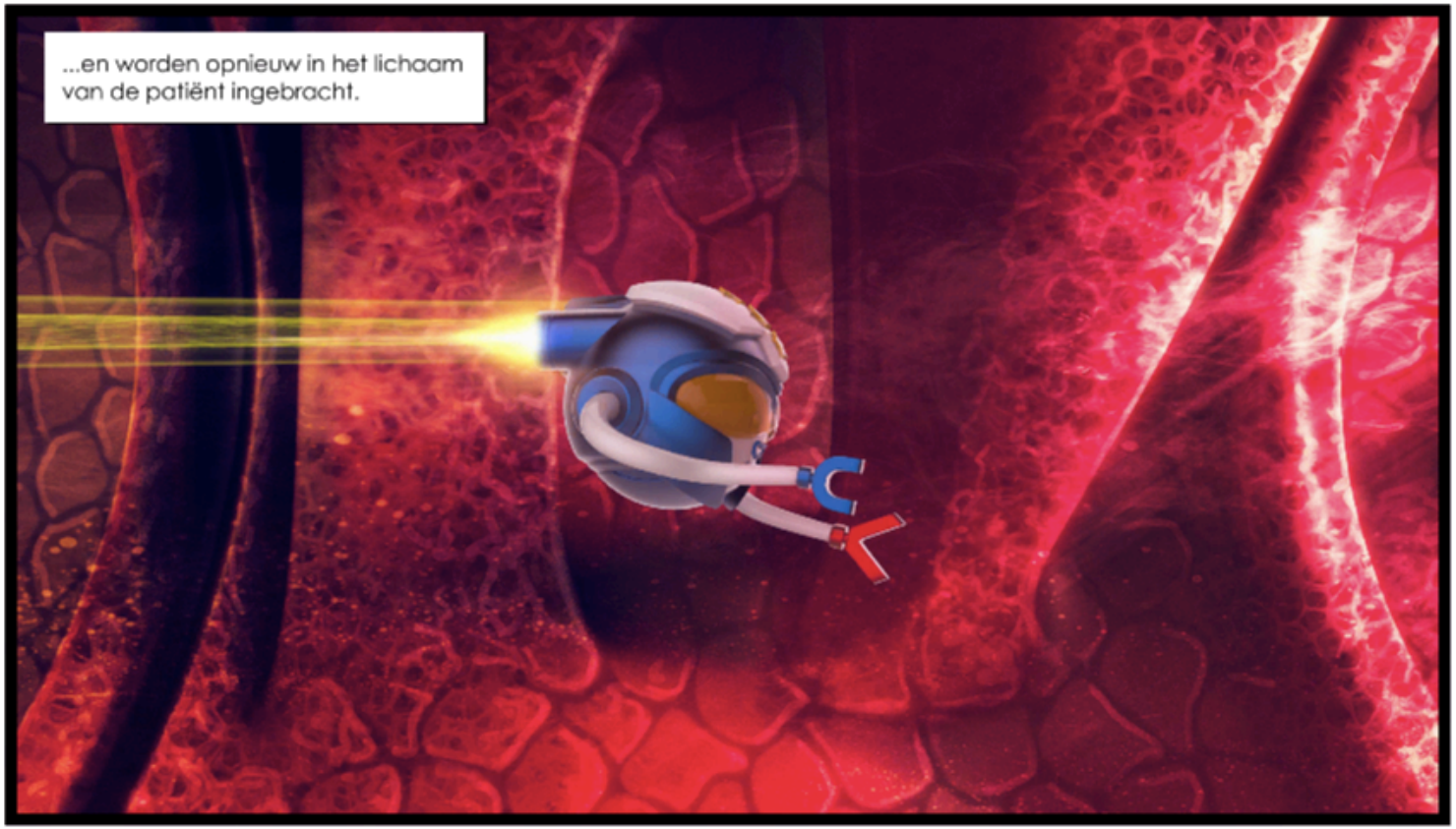
unity WebGL

immuno_web



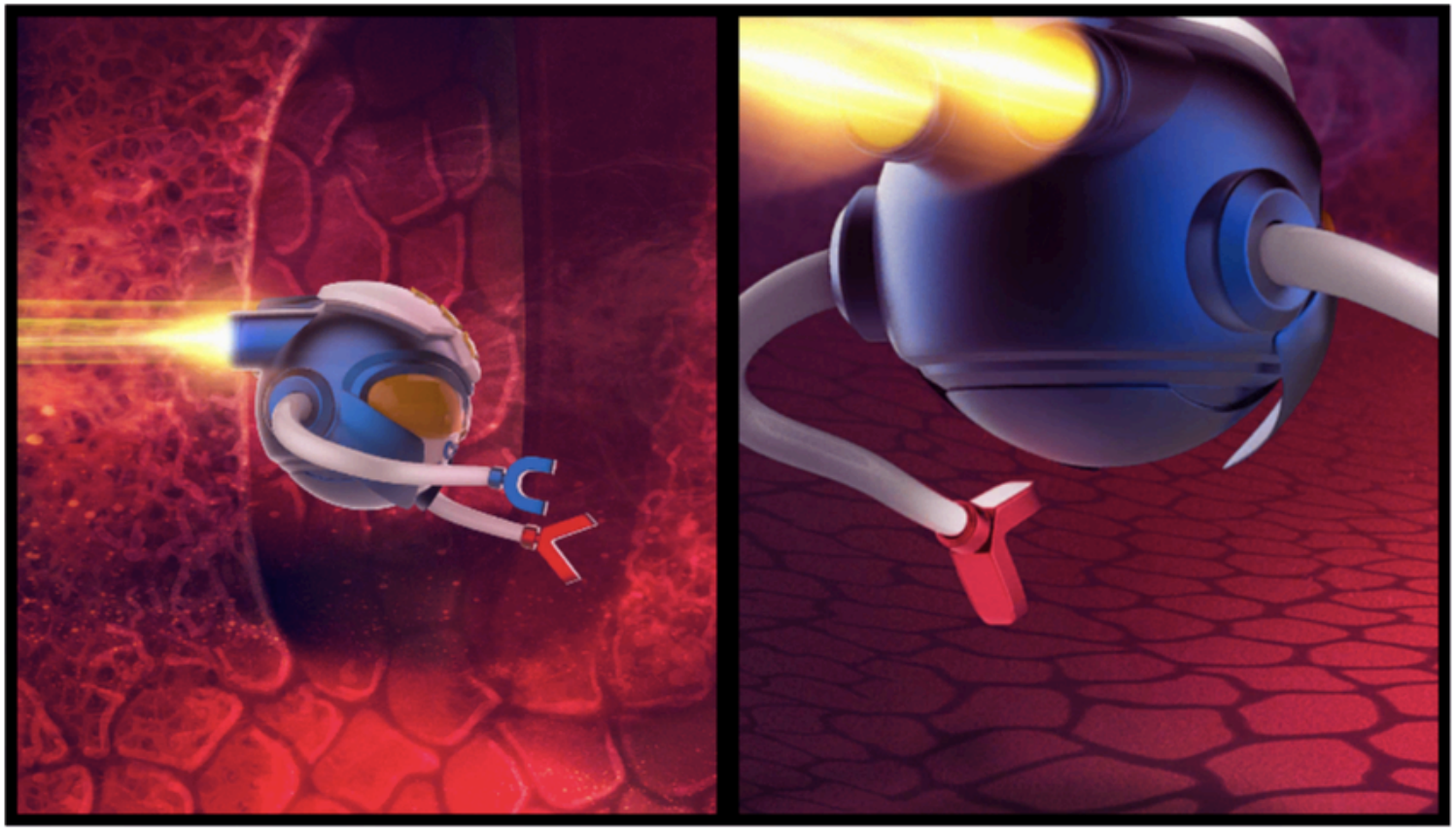
unity WebGL

immuno_web



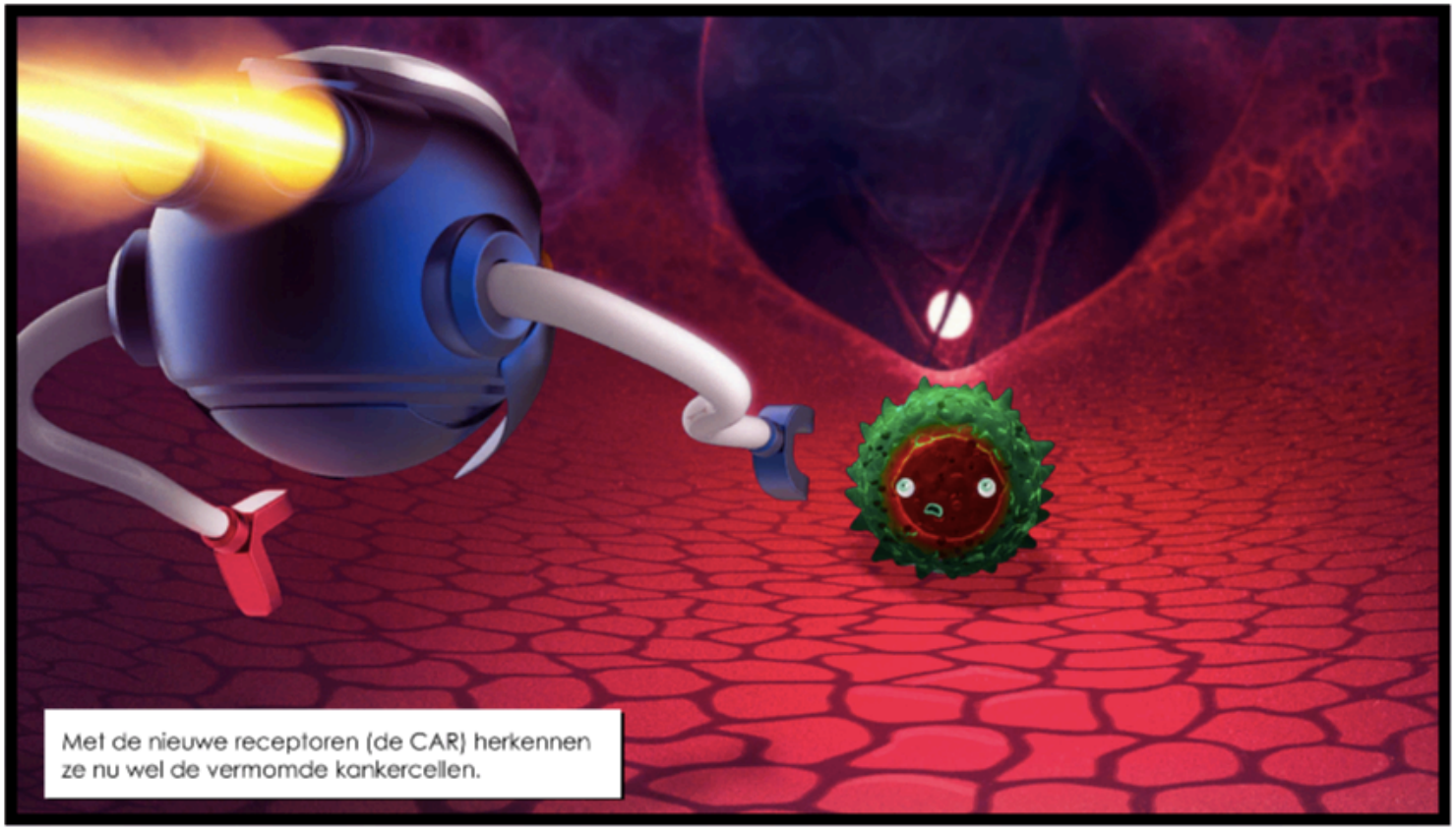
unity WebGL

immuno_web



unity WebGL

immuno_web

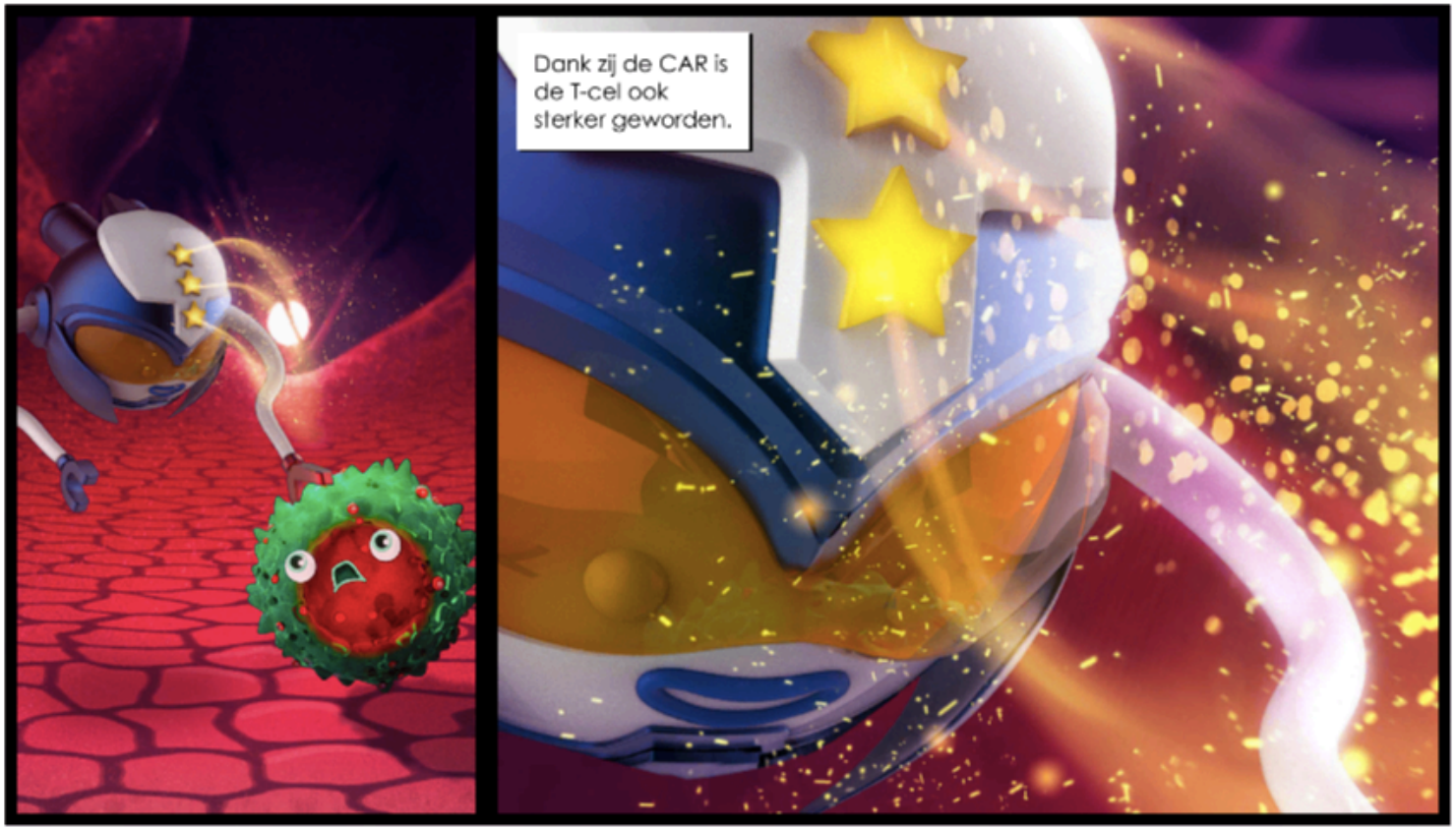


unity WebGL

immuno_web

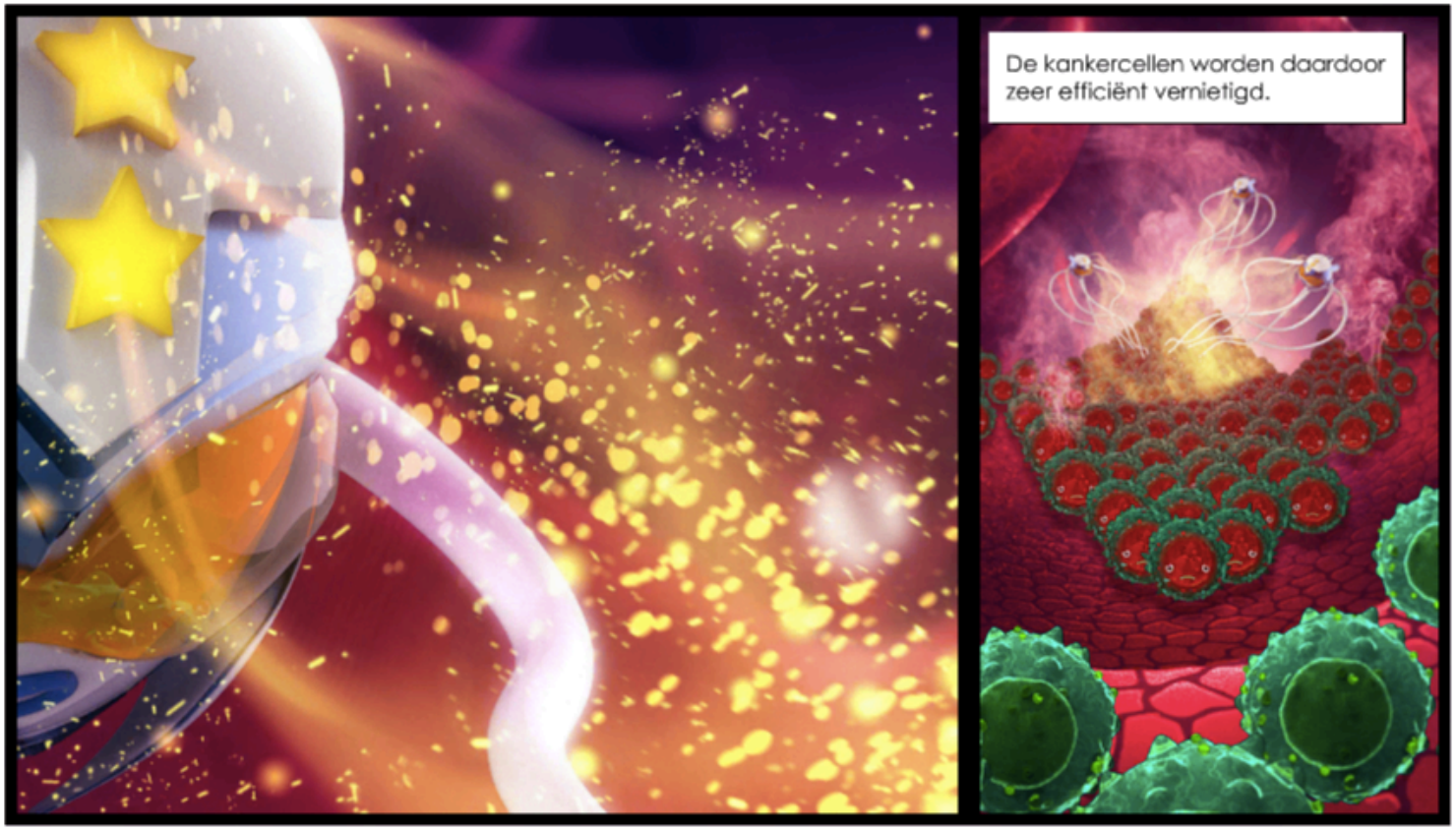
unity WebGL

immuno_web



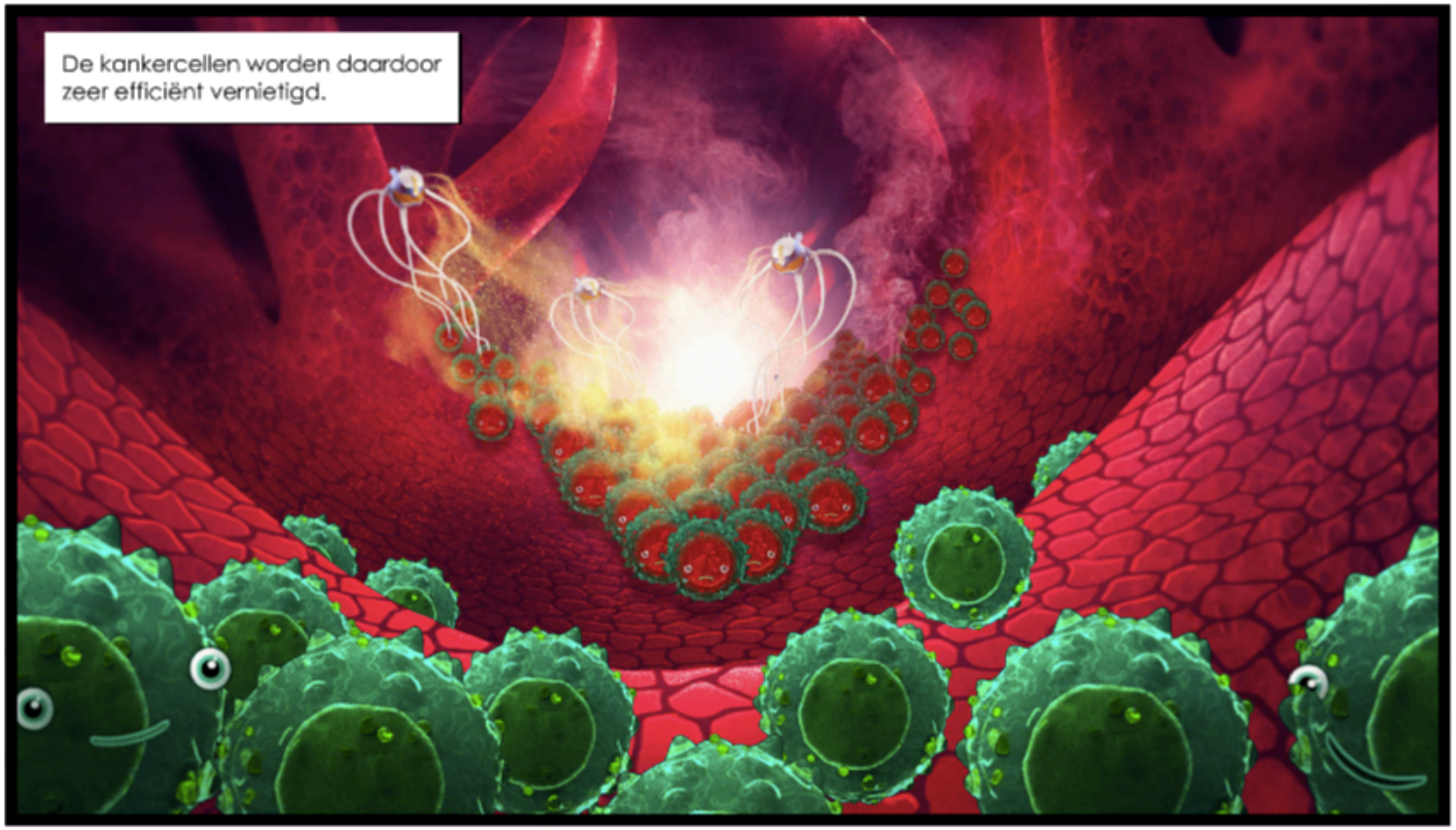
unity WebGL

immuno_web



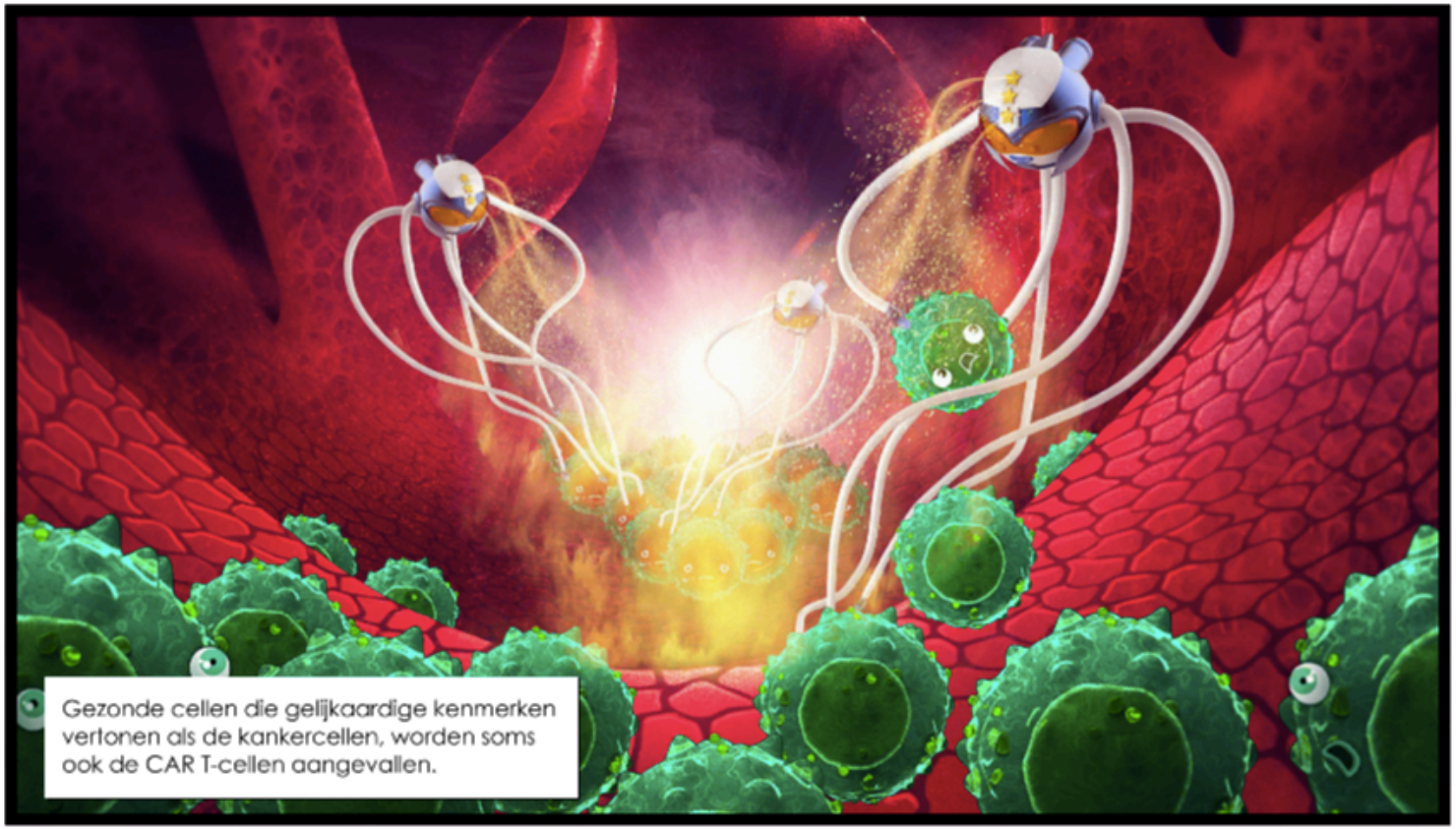
unity WebGL

immuno_web



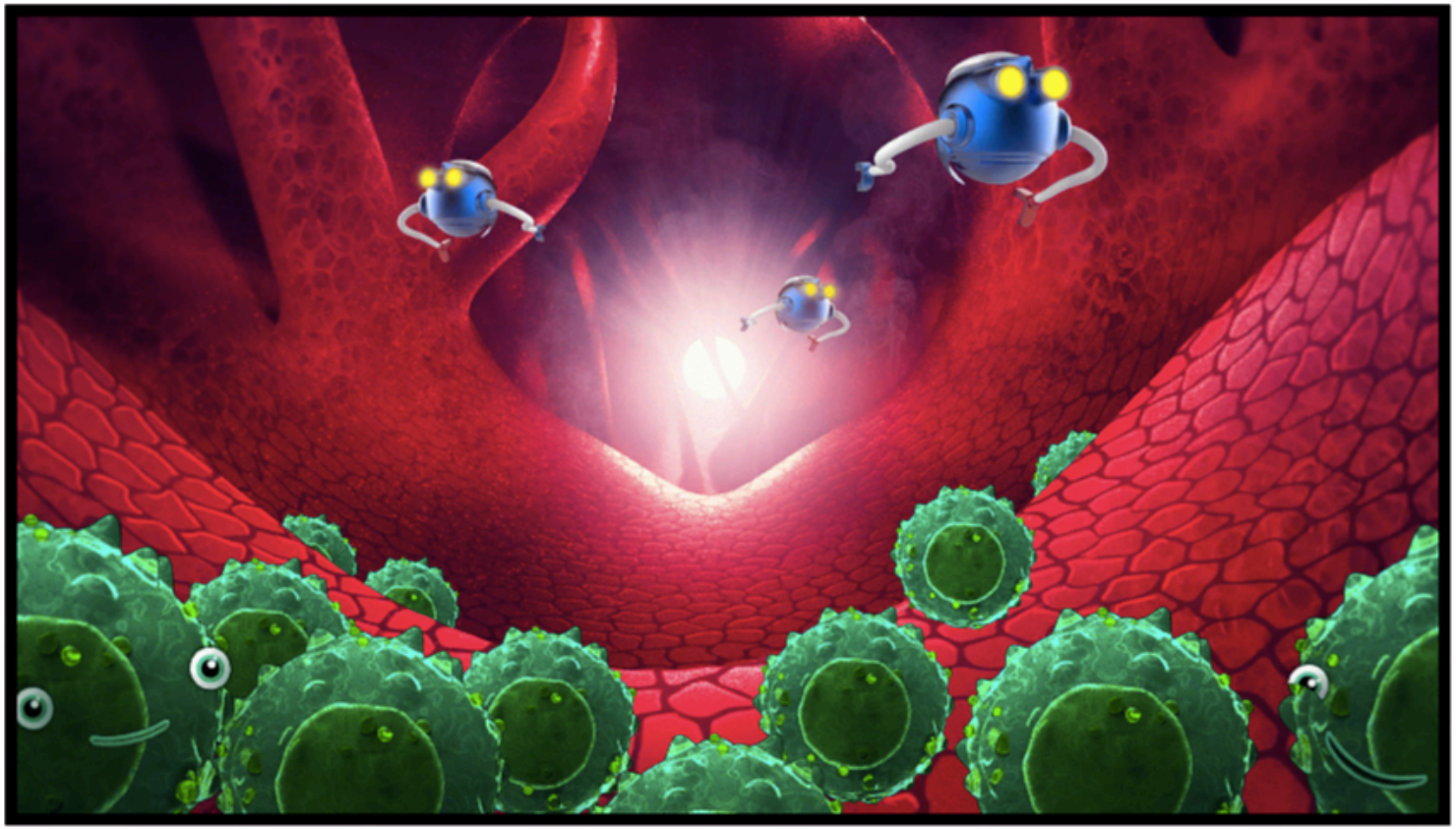
unity WebGL

immuno_web



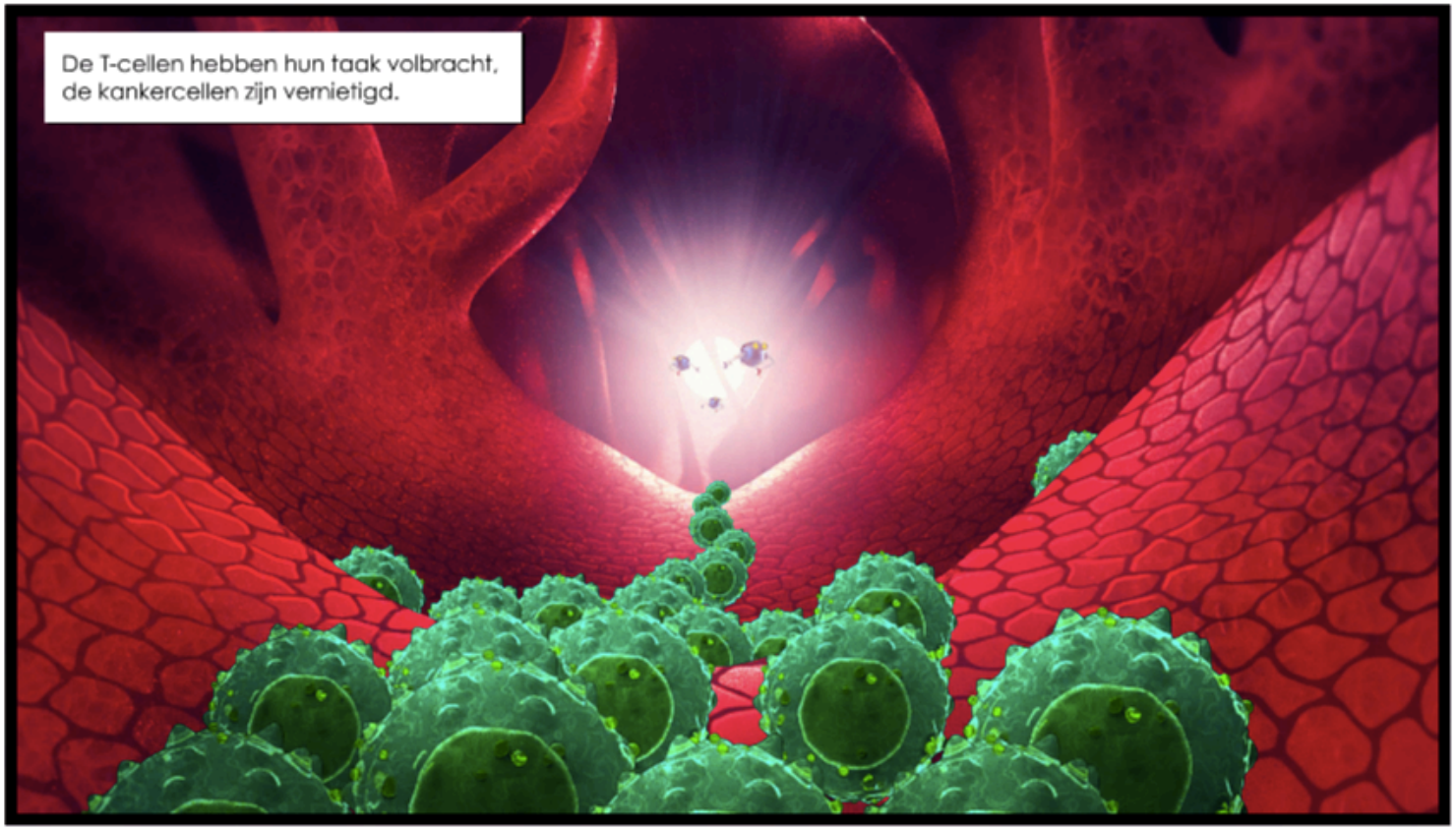
unity WebGL

immuno_web



unity WebGL

immuno_web



unity WebGL

immuno_web

CAR-T CEL THERAPIE

UNIVERSITEIT
GENT

CAR T-CEL THERAPIE

Emily

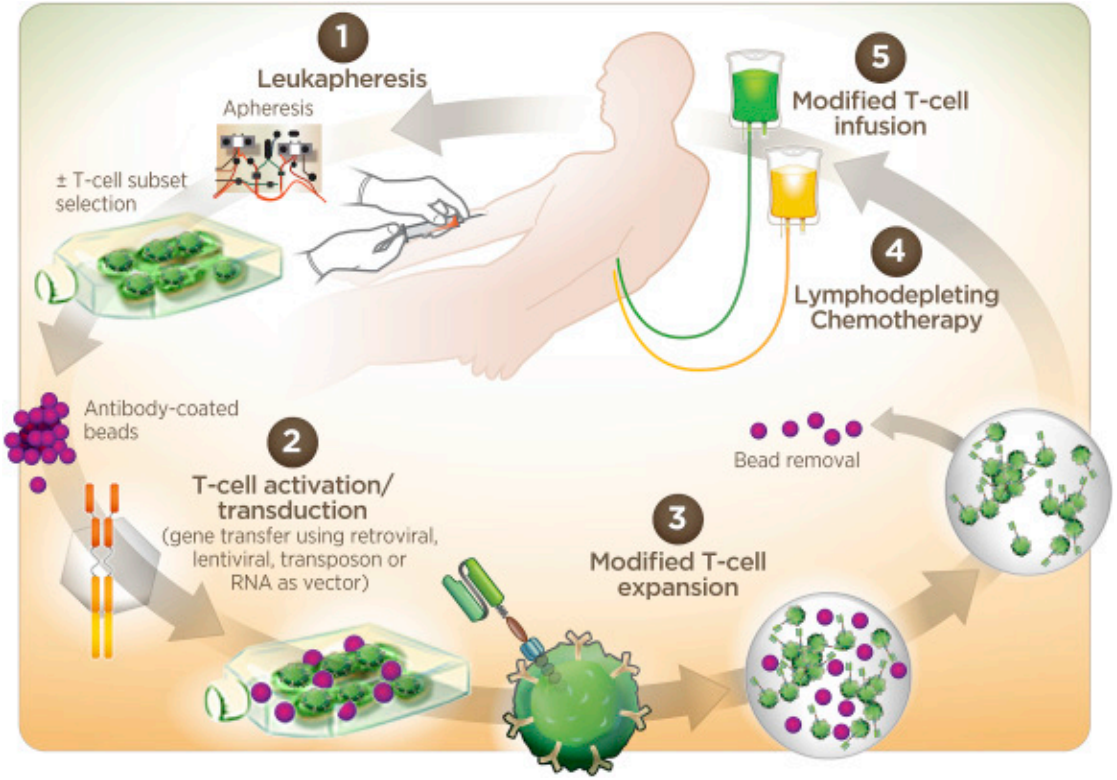
UNIVERSITEIT
GENT

CAR T-CEL THERAPIE

Emily

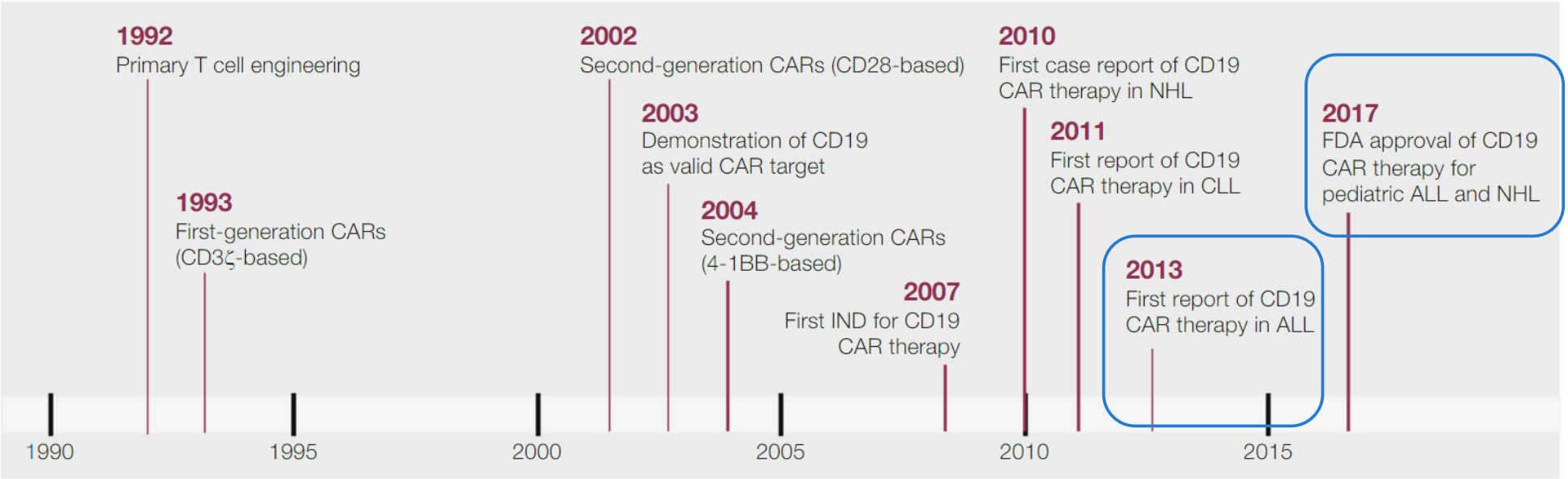
UNIVERSITEIT
GENT

CAR-T CEL THERAPIE



UNIVERSITEIT GENT

CD19 CAR-T: EEN PIONEER



References for further reading are available with this article online: www.cell.com/cell/abstract/10.1016/j.cell.2017.12.002

Sadelain, Cell, 2017

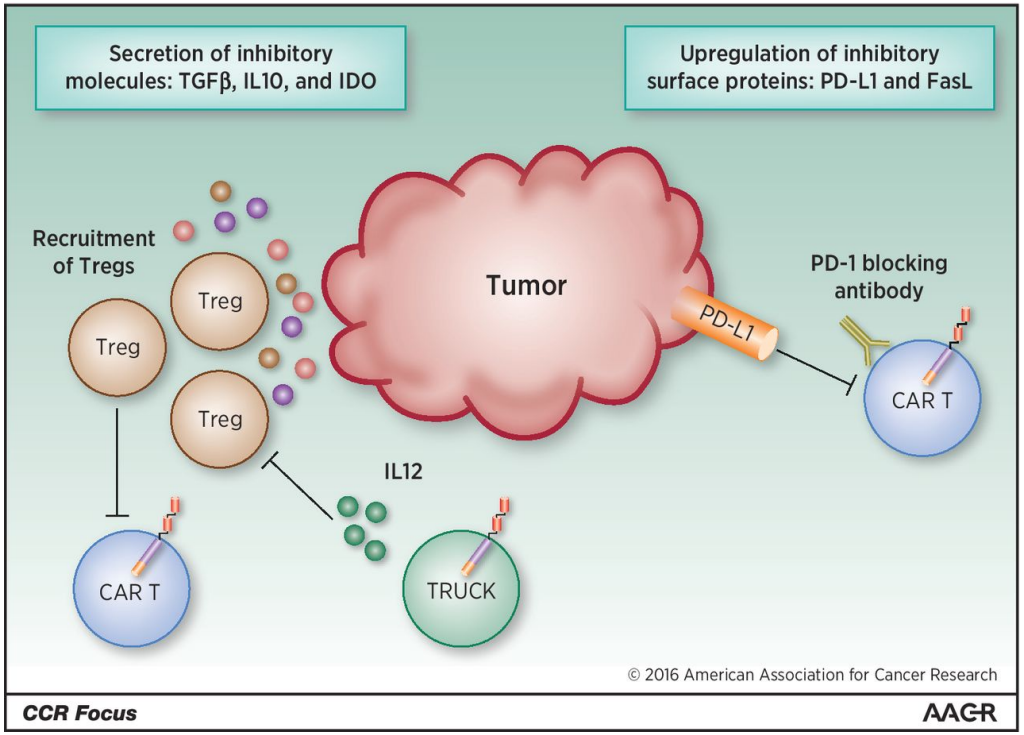
CAR-T-CEL THERAPIE

CAR T indicaties

- B cel maligniteiten (CD19, CD20, CD22)
- Multipel myeloom (CD138, BCMA, CD38, CD56, LeY)
- AML (CD33, 123, LeY, NKG2D liganden)
- Hodgkin lymfoom, T cel lymfoom (CD30)
- Solide tumoren
  - Refractair neuroblastoom
  - Andere: sarcoom, glioblastoom, mesothelioom, carcinoom (ovarium, colon, pancreas, nier)

CAR-T CEL THERAPIE VOOR SOLIDE TUMOREN

- Grotere uitdaging dan voor hematologische tumoren
  - Micro-omgeving: immuunsupprimerend
  - Heterogeen



Maus and June, Clin Cancer Res, 2016

EERSTE CAR-T THERAPIE TERUGBETAALD IN BELGIE

Hoop voor 140 kankerpatiënten: peperdure therapie wordt terugbetaald

23/05/2019 om 03:00 door Nina Bernaerts en Jonas Mayeur - Print - Corrigeer

(FOTO: TELEFACTS)

NIEUWS

Het Nieuwsblad, 23/05/2019

UNIVERSITEIT GENT

TERUGBETAALDE CAR-T IN BELGIE

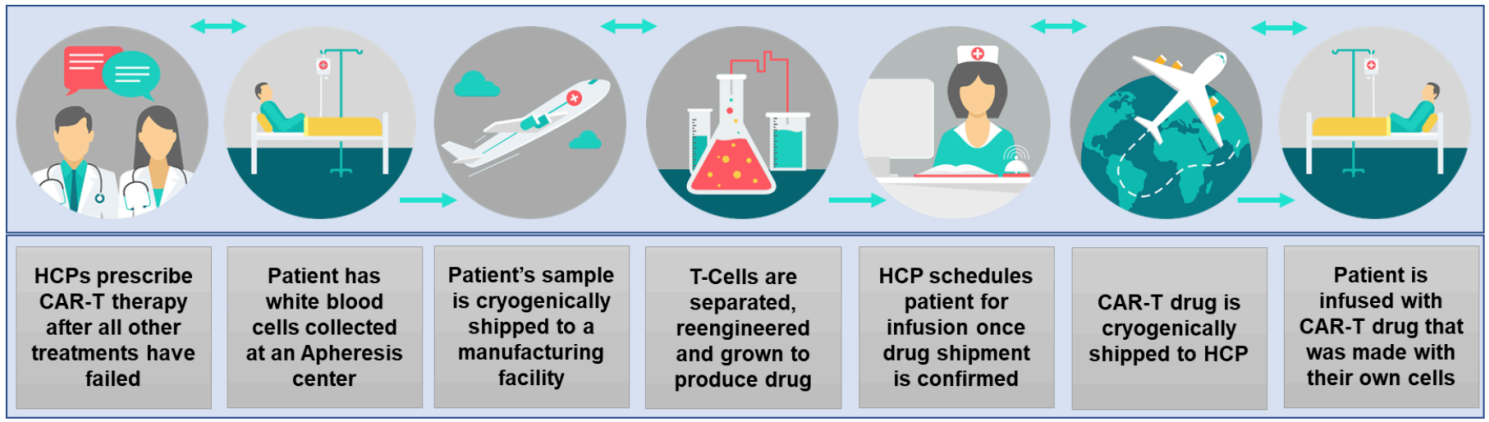
- **Kymriah (Novartis)**
- Centra: UZG, UZL, Ulg, UCL (total in Belgium: n=9)
- Indicaties
  - B-ALL: vanaf 2de relapse
  - DLBCL: na minstens 2 lijnen therapie
- UZG:
  - B-ALL (n=4, 1 adult, 3 pediatric)
  - DLBCL (n=2)

- Coming soon (we hope): **Yescarta (Gilead)**

UNIVERSITEIT GENT

UITDAGINGEN VOOR CAR-T THERAPIE

– Logistieke uitdagingen van een complex proces



Demand forecasting & Scheduling

Network Design & Capacity Planning
Process engineering & Manufacturing Technology

Service operations
Billing/Invoicing

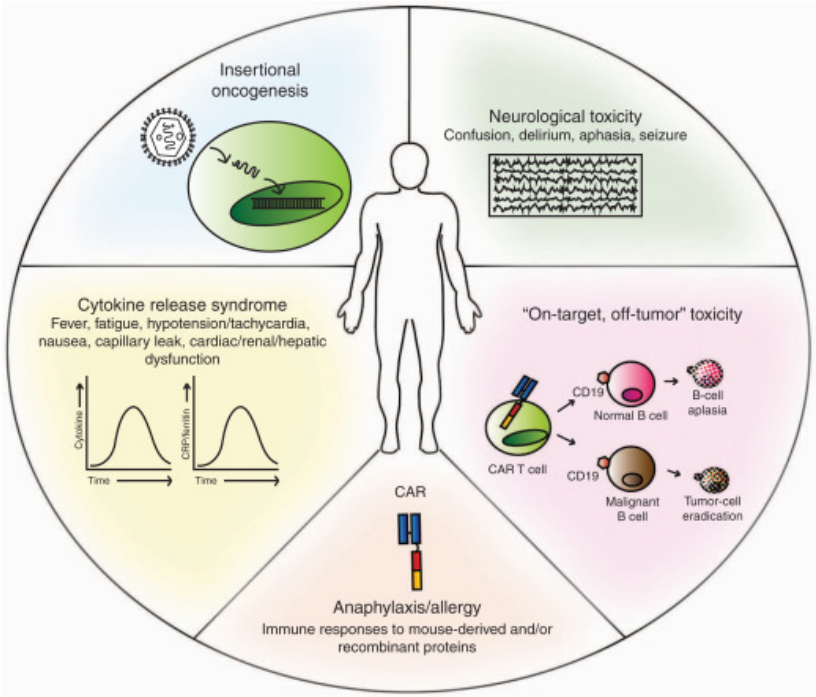
End-End Tracking, Visibility, and Coordination

UNIVERSITEIT GENT

Shankar Suryanarayanan et al, Pharmexec.com

CAR-T-CEL THERAPIE

– Bijwerkingen

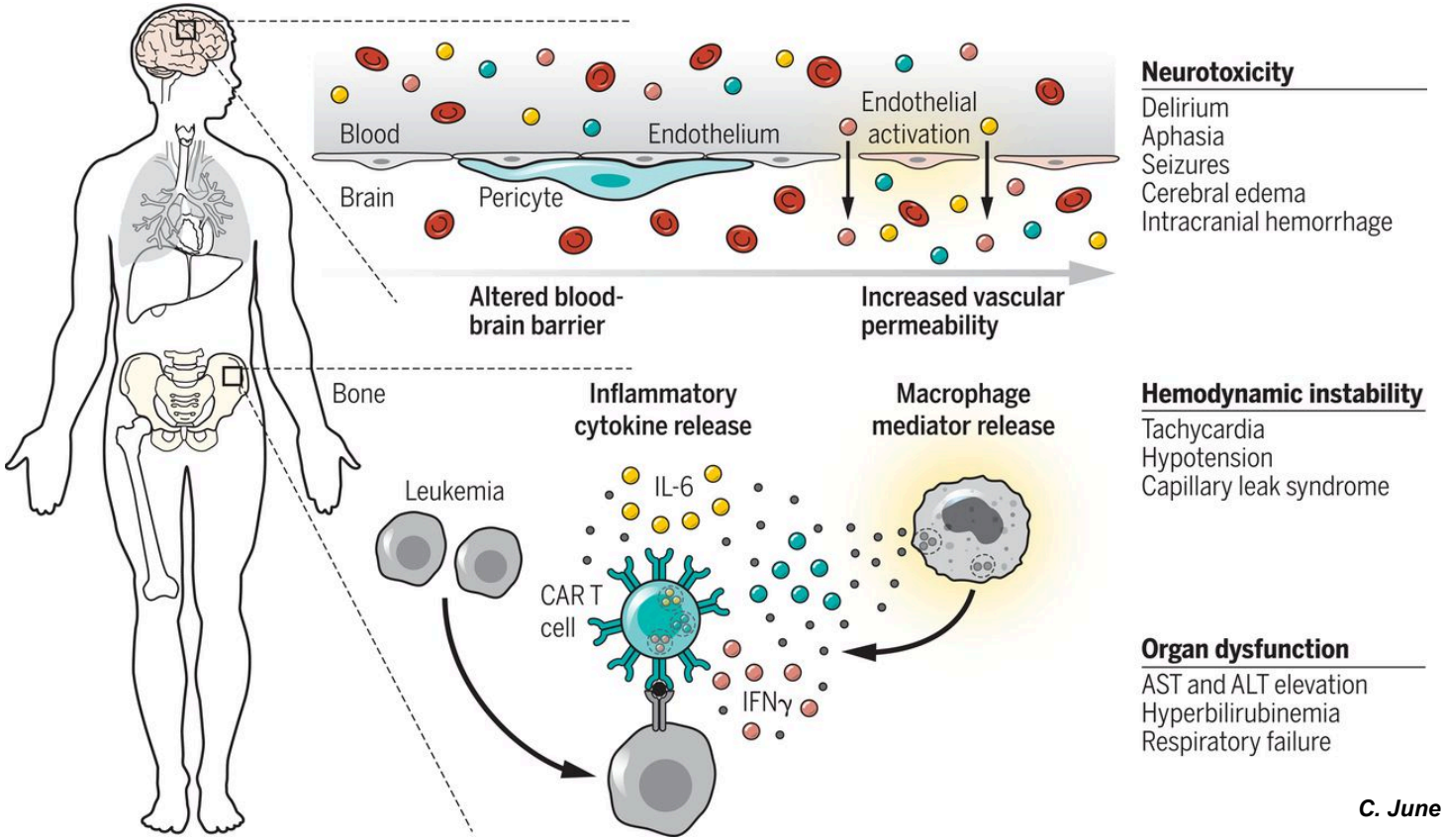


UNIVERSITEIT GENT

C. Bonifant et al, 2018 62

CAR-T-CEL THERAPIE

– Bijwerkingen

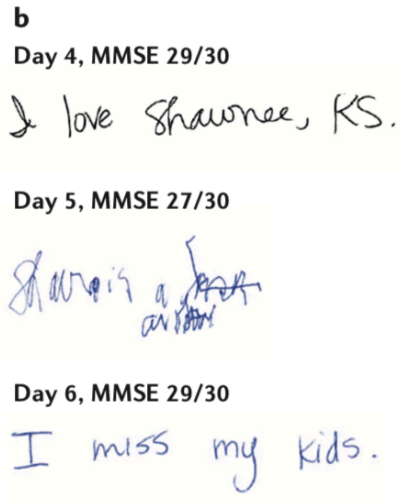


C. June et al, 2018

CAR-T-CEL THERAPIE

CAR-T: bijwerkingen

– **CRES: scoring**



CARTOX-10 CRES score

Normale cognitieve functie: 10/10

1, Welk jaar zijn we? (1pt)

2, Welke maand zijn we? (1 pt)

3, In welke stad zijn we? (1 pt)

4, In welk ziekenhuis zijn we? (1 pt)

5, Wie is de eerste minister van België? (1 pt)

6, benoem 3 objecten (die de interviewer aanduidt) (3 pt)

7, schrijf een korte zin (bv het UZ Gent is het coolste ziekenhuis ter wereld.) (1 pt)

8, tel terug vanaf 100 (in tientallen) (1 pt)

UNIVERSITEIT GENT

S. Neelapu et al, 2018

CAR-T-CEL THERAPIE

CAR-T: bijwerkingen

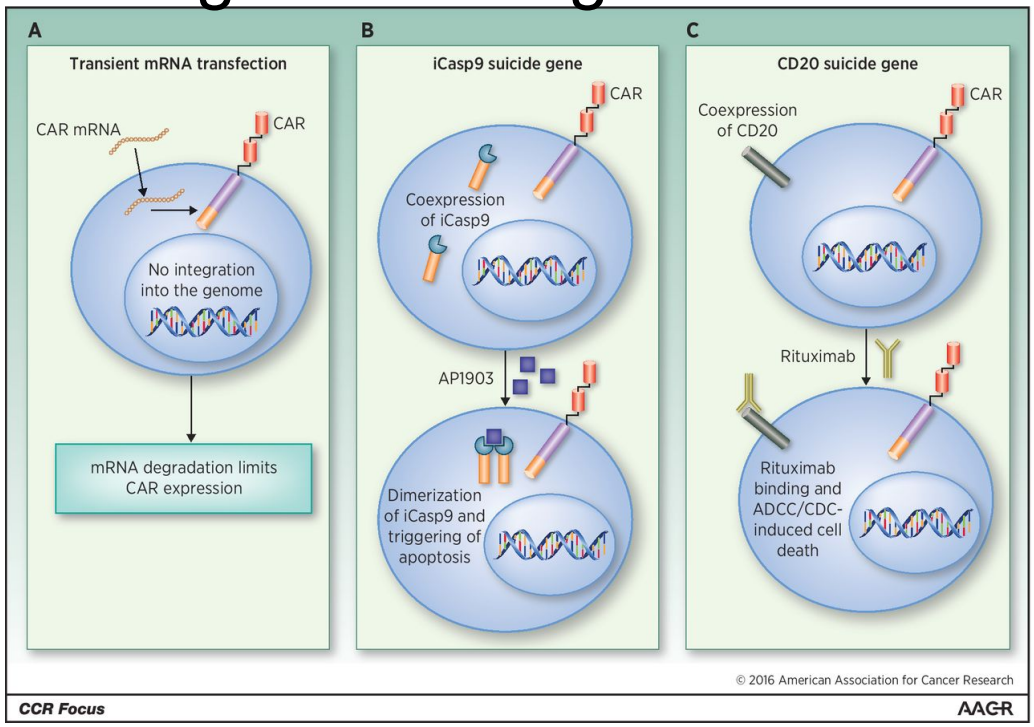
- Opname vs dichtbij ziekenhuis: Hotels? Hoelang?
- On-target, off-tumor: aanvallen van gezonde cellen
- Het grote onbekende: opvolging 15 jaar (GGO!)
- …

UNIVERSITEIT GENT

S. Neelapu et al, 2018

CAR-T-CEL THERAPIE

– Veiligheid verhogen

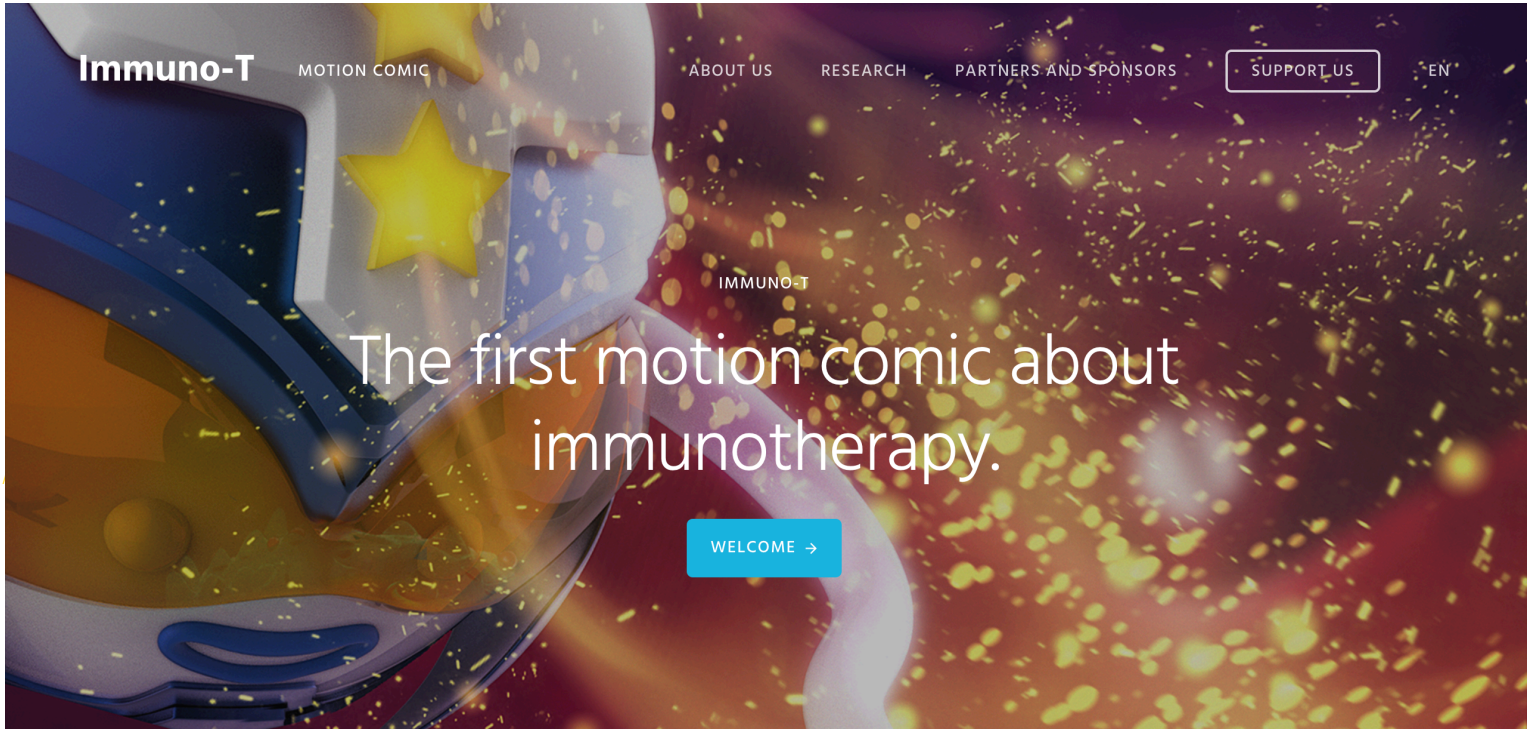


UNIVERSITEIT GENT

Maus and June, Clin Cancer Res, 2016

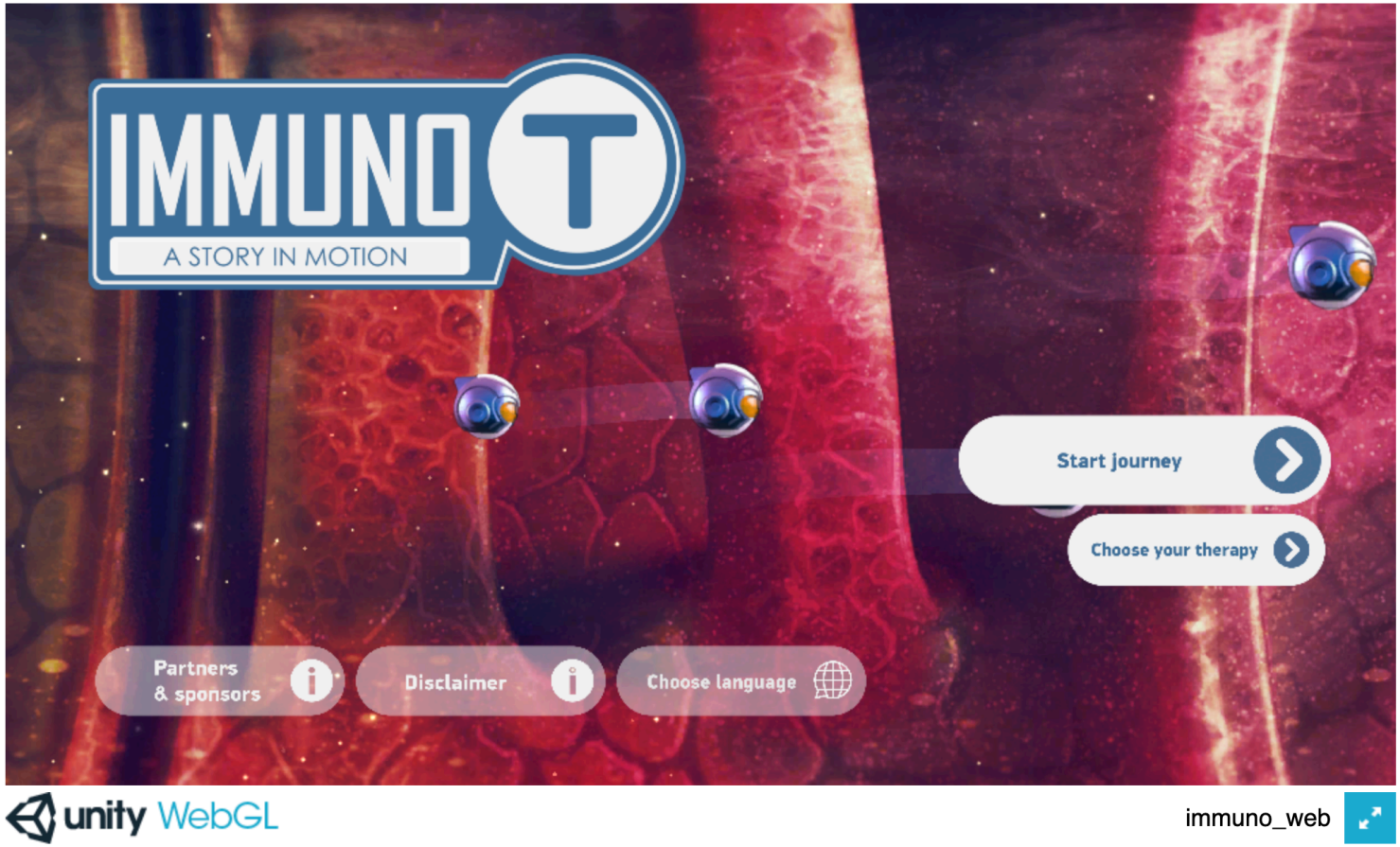
CAR-T-CEL THERAPIE

– Patiënt educatie



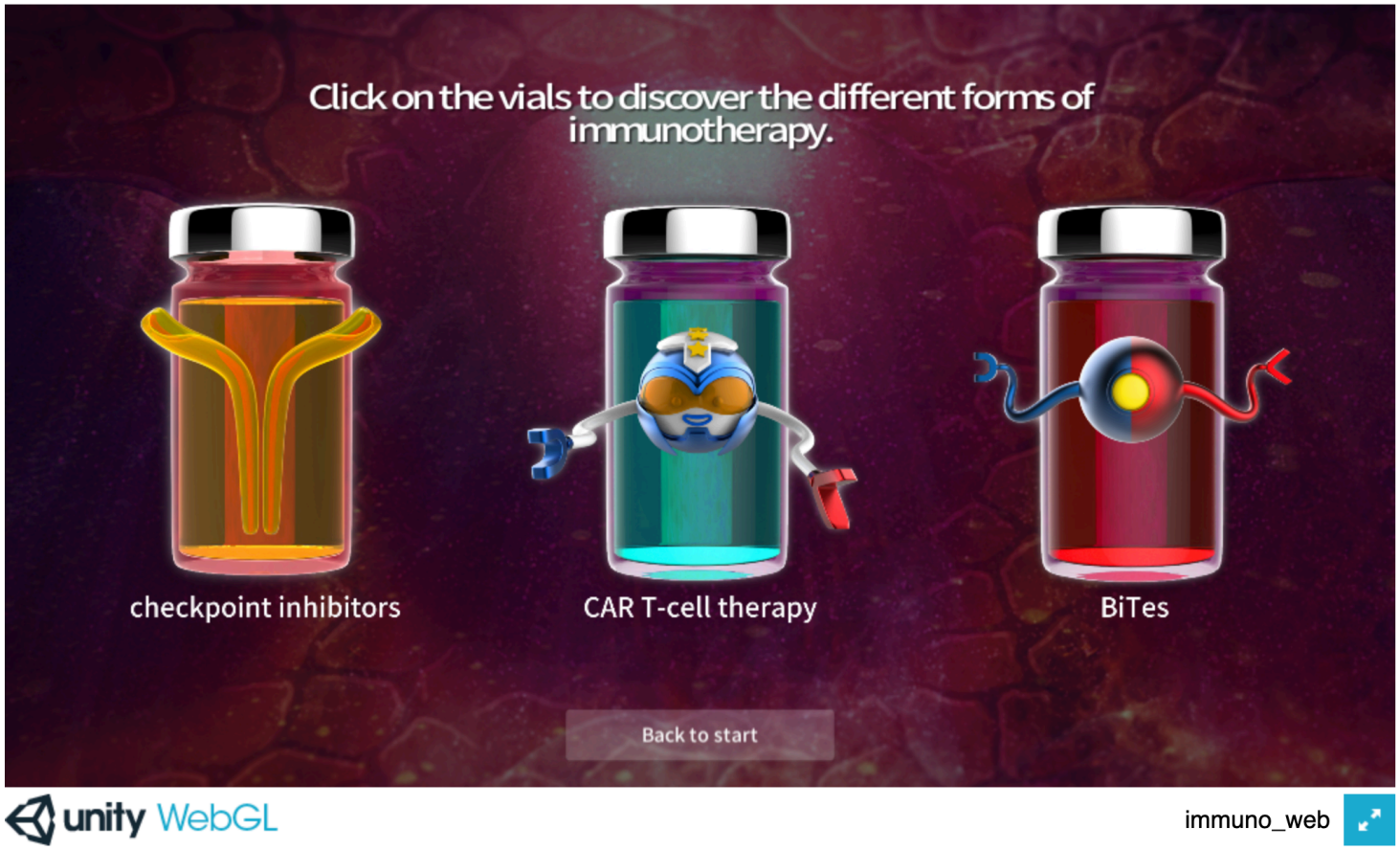
CAR-T-CEL THERAPIE

– Patiënt educatie



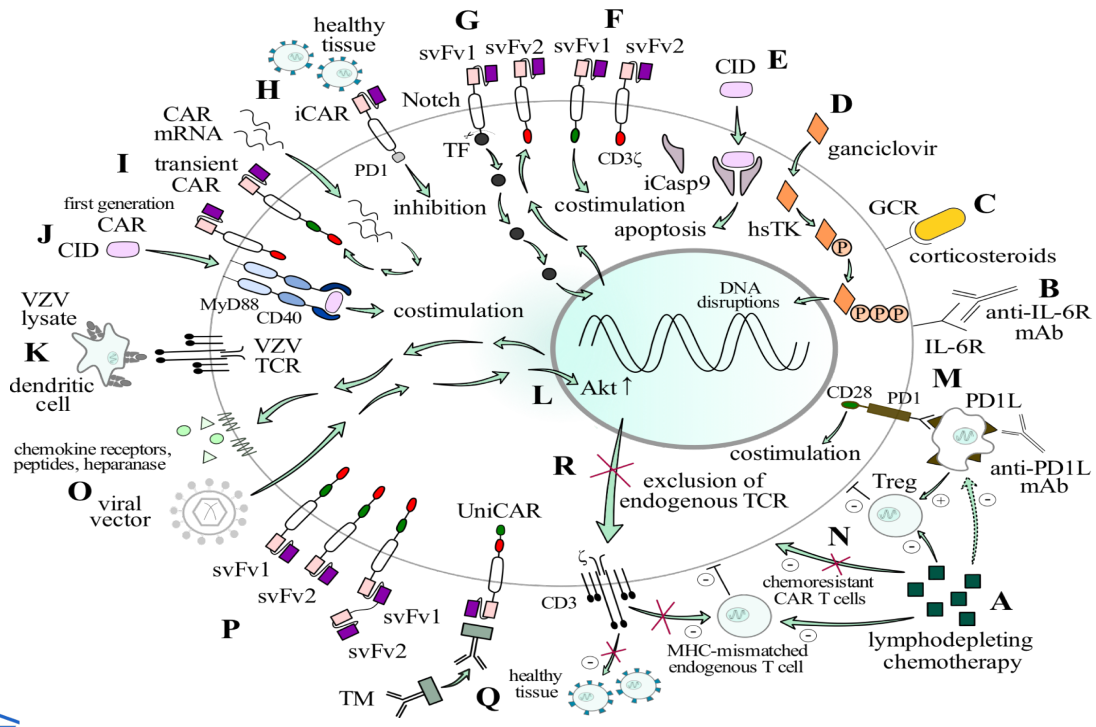
CAR-T-CEL THERAPIE

– Patiënt educatie



CAR-T-CEL THERAPIE

– Nieuwe concepten in CAR-T design



UNIVERSITEIT GENT

Van Schandevyl S & Kerre T, Acta Clinica Belgica, 2018

CAR-T-CEL THERAPIE

Wat brengt de toekomst?

- Financiële toxiciteit: goedkoper (allogene off-the-shelf, home made CARs, Chinese CARs…)
- Veiliger
- Meer doelwitten
- Combinatie met andere therapie, zelfs andere immunotherapie
- …

UNIVERSITEIT
GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Tessa Kerre

Hematoloog UZ Gent
Hoofddocent UGent

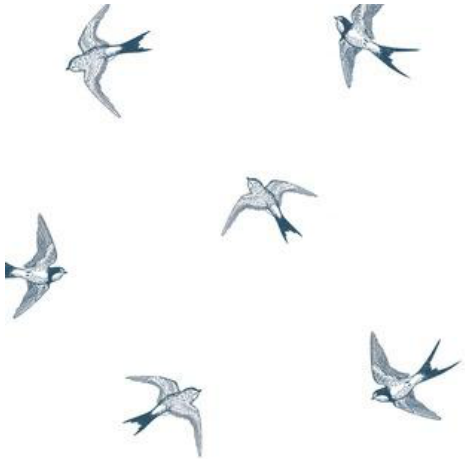
DIENST HEMATOLOGIE
E tessa.kerre@ugent.be
T +32 9 332 66 54

Ghent University
@ugent
Ghent University

www.ugent.be
Immuno-T.inmotion.care

UNIVERSITEIT GENT

UNIVERSITEIT GENT



"One swallow is a coincidence, but two swallows make summer."
— Siddhartha Mukherjee, The Emperor of All Maladies: A Biography of Cancer