



FACULTEIT GENEESKUNDE EN
GEZONDHEIDSWETENSCHAPPEN

DIENST HEMATOLOGIE UZ GENT



IMMUNOTHERAPIE VOOR KANKER: HYPE OF HOOP?

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

MELANOOMPUNT - 29 JANUARI 2022

Prof. Dr. Tessa Kerre



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HET VERHAAL VAN EMILY



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HET VERHAAL VAN EMILY



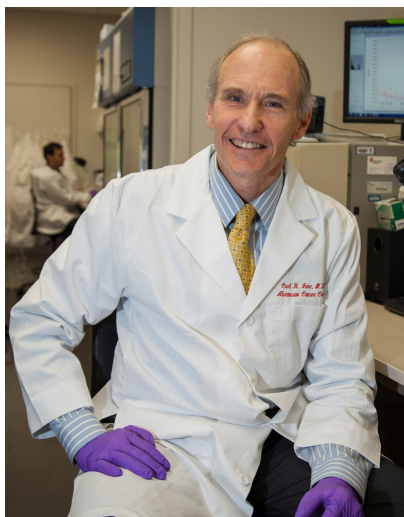
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HET VERHAAL VAN EMILY



Carl June

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Emily Whitehead

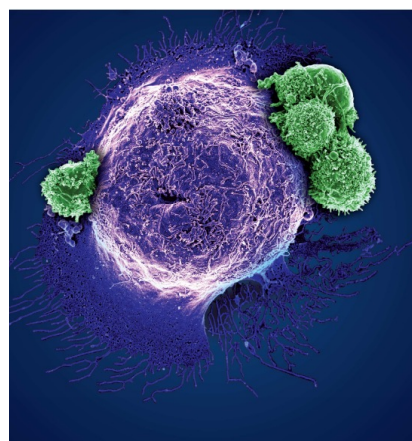
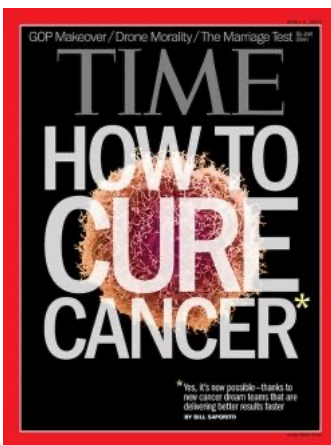
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IMMUNOTHERAPIE



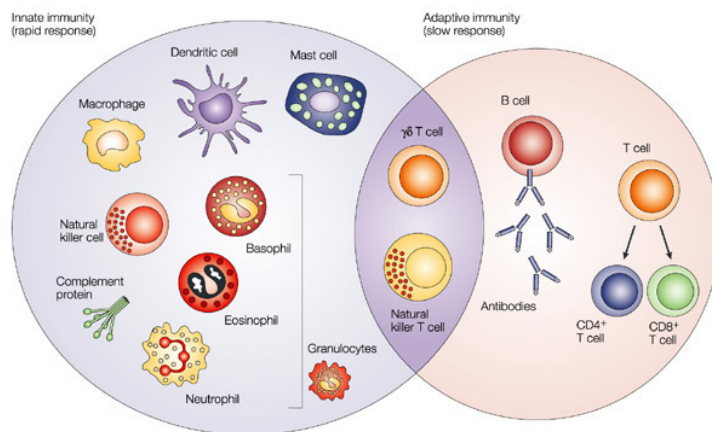
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HET IMMUUNSYSTEEM EN KANKER

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HET IMMUUNSYSTEEM

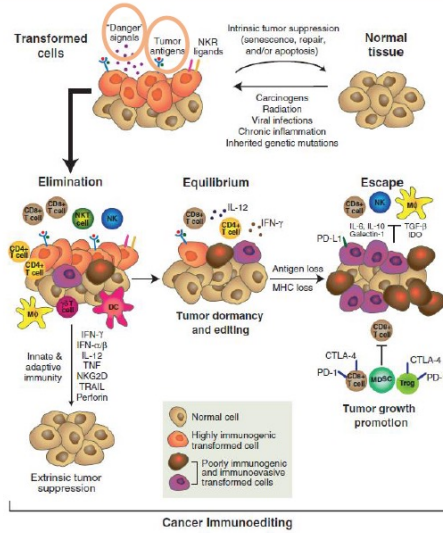


Nature Reviews | Cancer

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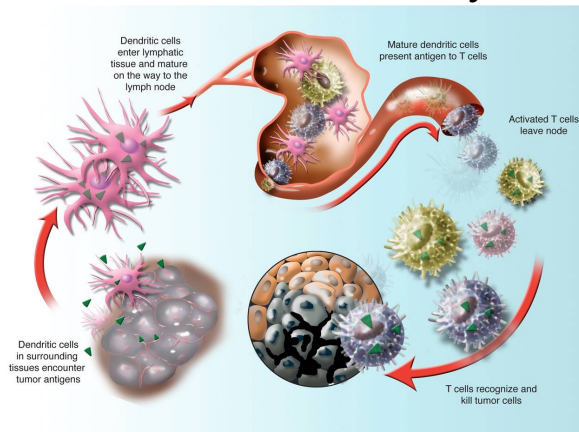
HET IMMUNUSYSTEEM EN KANKER

– Interacties immuunsysteem en kanker



HET IMMUNUSYSTEEM EN KANKER

– Interacties immuunsysteem en kanker



HET IMMUUNSYSTEEM EN KANKER

– De kanker – immuunsysteem cyclus

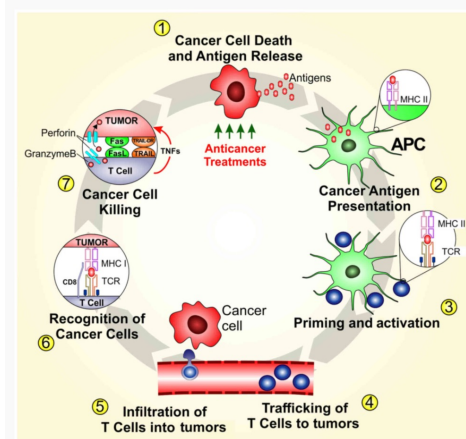


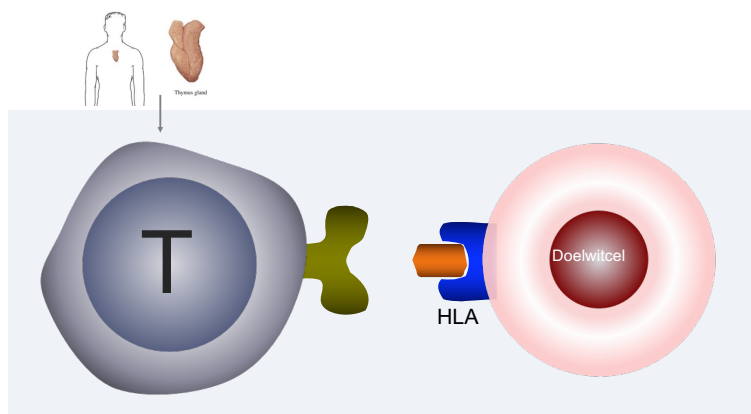
Figure 1 - The cancer immunity cycle.
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G Leonardi et al, In J Oncol, 2020¹¹

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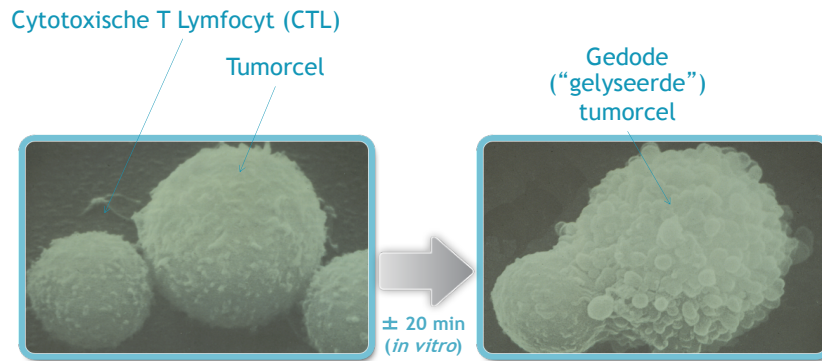
HET IMMUUNSYSTEEM EN KANKER

– T cellen herkennen doelwitcel



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HET IMMUUNSYSTEEM EN KANKER



WAAROM ONTSNAPT KANKER AAN HET IMMUUNSYSTEEM?

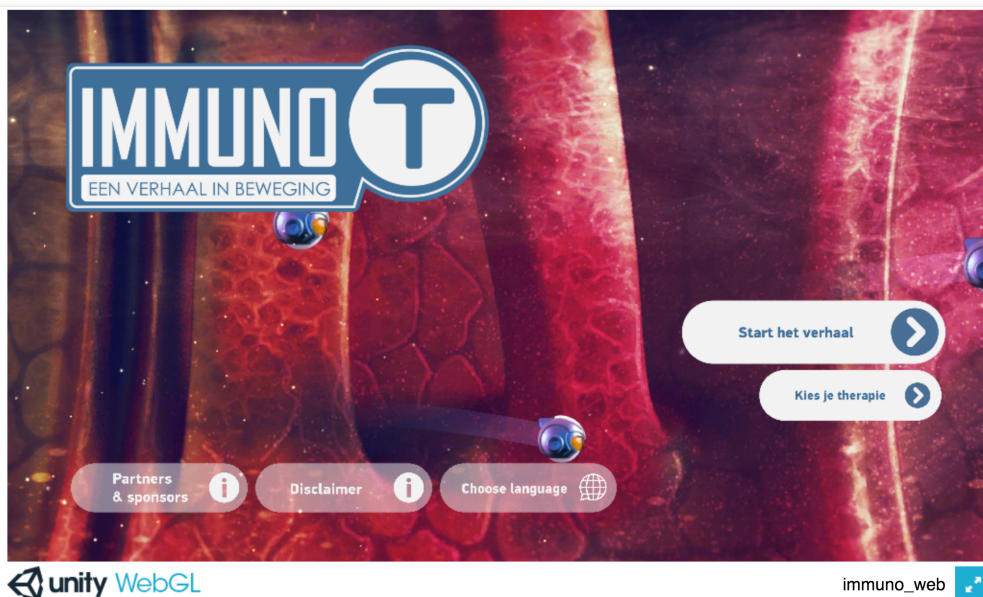
- **Falend immuunsysteem**
 - T cellen die tumor herkennen zijn afwezig
 - Het immuunsysteem faalt: patiënten die immuunsuppressiva nemen, AIDS, chemotherapie/radiotherapie, ...
- **Tumor onderdrukt het immuunsysteem**
 - Verdwijnen van tumorantigenen en/of HLA molekulen op het celoppervlak van de tumorcellen
 - Aantrekken van cellen en oplosbare factoren die immuunreacties 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

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HET VERHAAL VAN IMMUNO-T: EN ZE LEEFDEN...



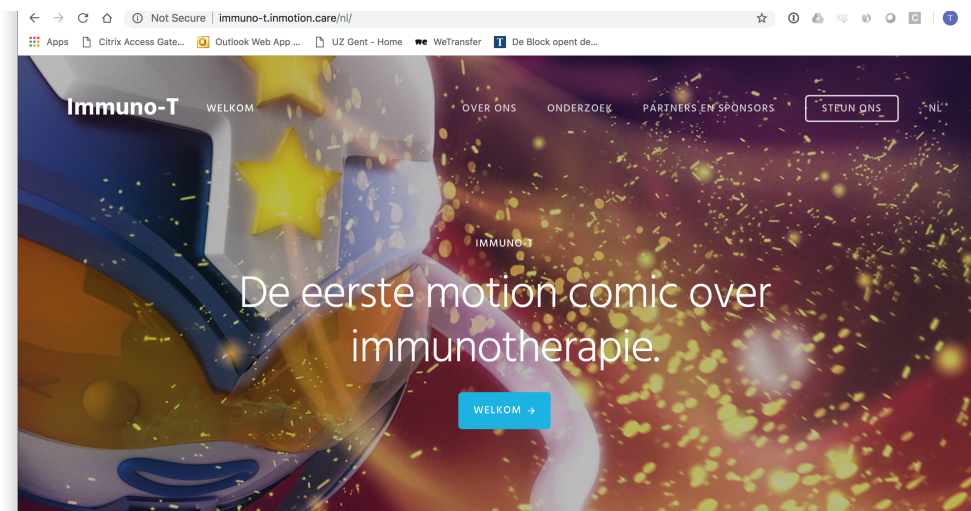
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HET VERHAAL VAN IMMUNO-T: EN ZE LEEFDEN



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HET VERHAAL VAN IMMUNO-T: EN ZE LEEFDEN...



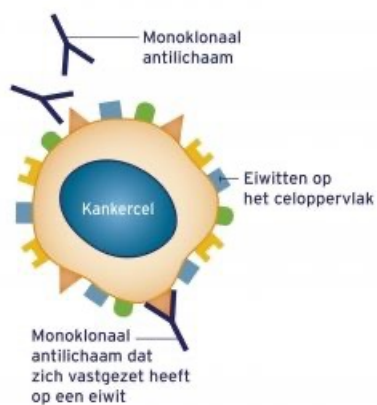
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OVERZICHT: IMMUNOTHERAPIE

- **Monoklonale antistoffen**
- **Vaccinatie**
 - Tumorextract
 - Peptide of mengsels van peptiden
 - Peptide gebonden op dendritische cellen
- **Oncolytische virussen**
- **Checkpoint inhibitoren**
- **Allogene stamceltransplantatie**
- **T cel therapie**
 - TCR/CAR transductie van circulerende T cellen
 - Antigen specifieke T cellen maken uit stamcellen

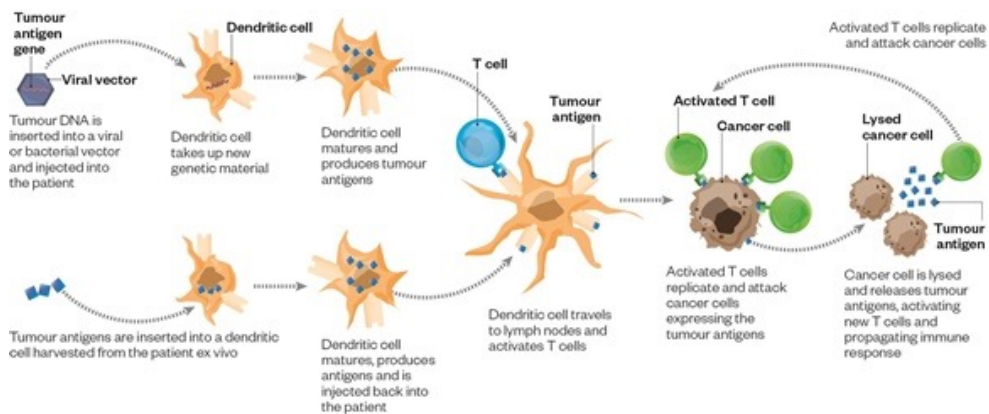
MONOKLONALE ANTISTOFFEN

– Principe



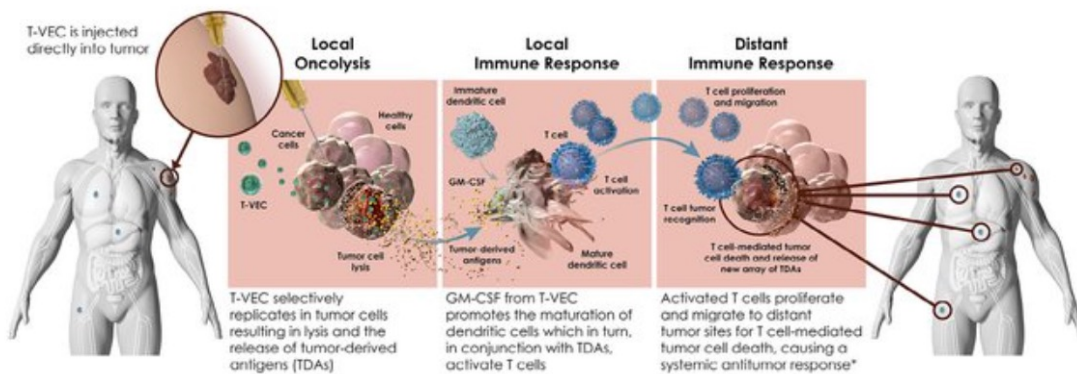
VACCINATIE

– Principe



ONCOLYTISCHE VIRUSSEN

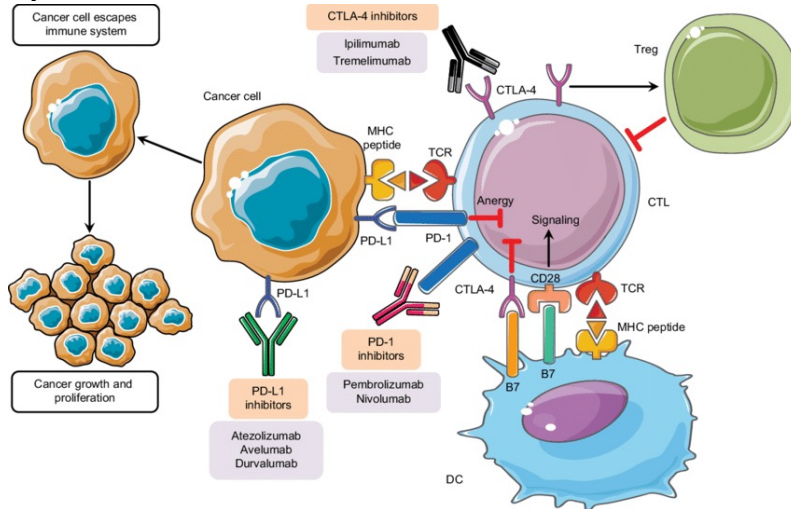
– Principe



*This figure depicts the proposed mechanism of action and is not meant to imply clinical efficacy.

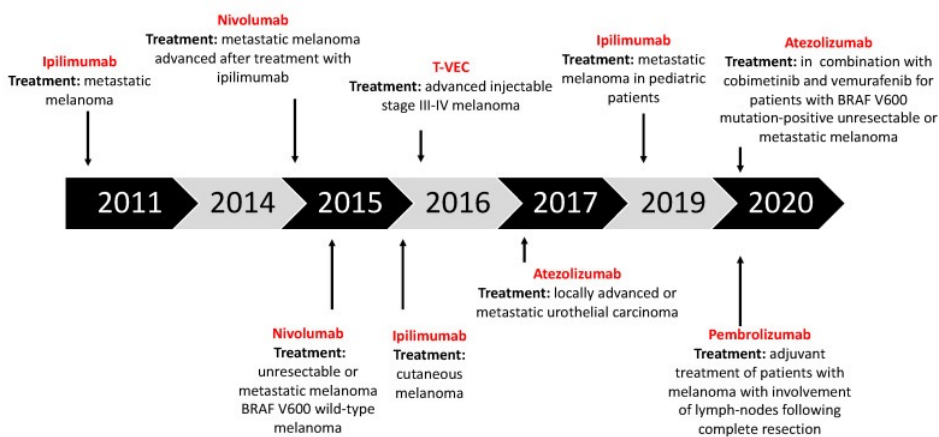
CHECKPOINT INHIBITOREN

– Principe



N Ayoub et al, Breast cancer: targets and therapy, 2019 23

IMMUNOTHERAPIE VOOR MELANOOM



L Kuryk et al, Cancers, 2020



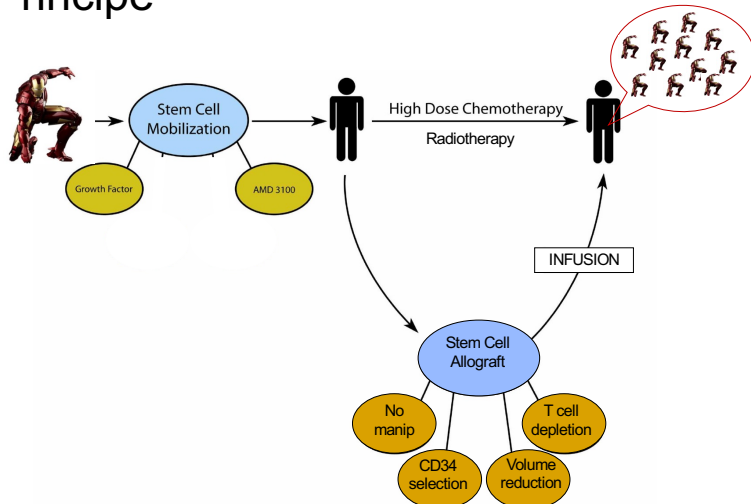
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- **T cel therapie**
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 - Antigen specifieke T cellen maken uit stamcellen

ALLOGENE STAMCELTRANSPLANTATIE

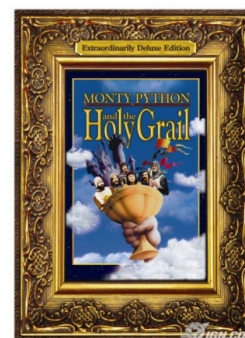
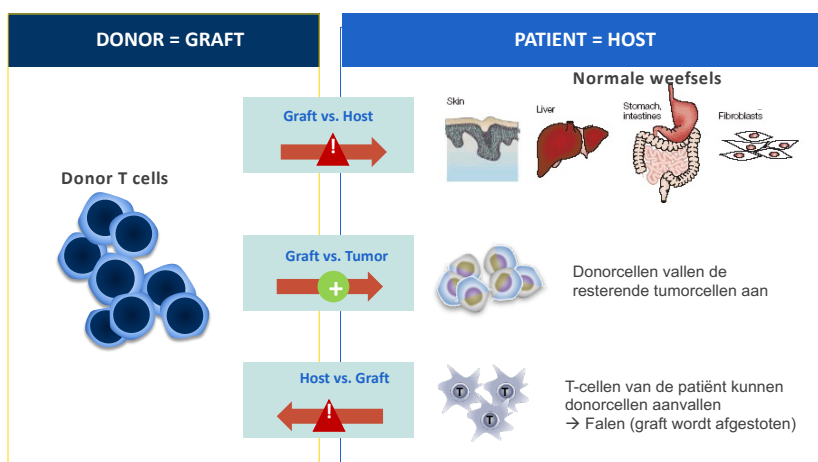
ALLOGENE STAMCELTRANSPLANTATIE

– Principe



ALLOGENE STAMCELTRANSPLANTATIE

– Graft vs Host en Host vs Graft reacties



ALLOGENE STAMCELTRANSPLANTATIE

– Graft vs Host en Host vs Graft reacties



ALLOGENE STAMCELTRANSPLANTATIE





ALLOGENE STAMCELTRANSPLANTATIE




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T-CEL THERAPIE

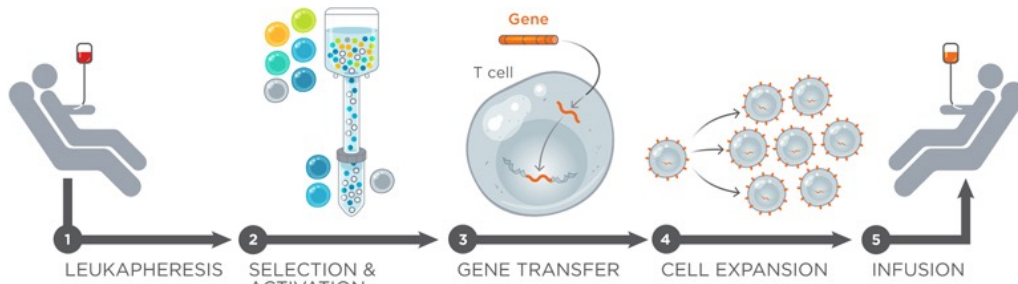

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T-CEL THERAPIE

– Genetisch gemodificeerde T-cellen

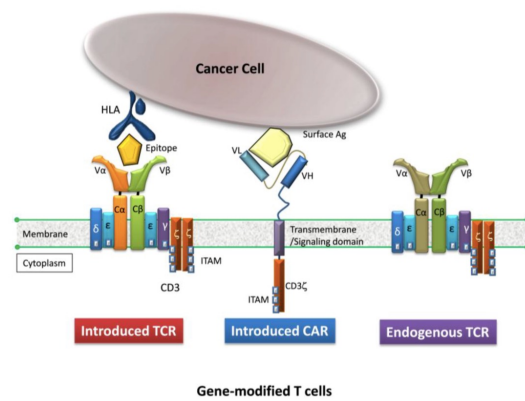


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T-CEL THERAPIE

– CAR/TCR



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Klik op de flesjes om de verschillende vormen van immuotherapie te ontdekken.

checkpoint inhibitoren

CAR T-cel therapie

BiTcs

TERUG NAAR HET BEGIN

unity WebGL

immuno_web

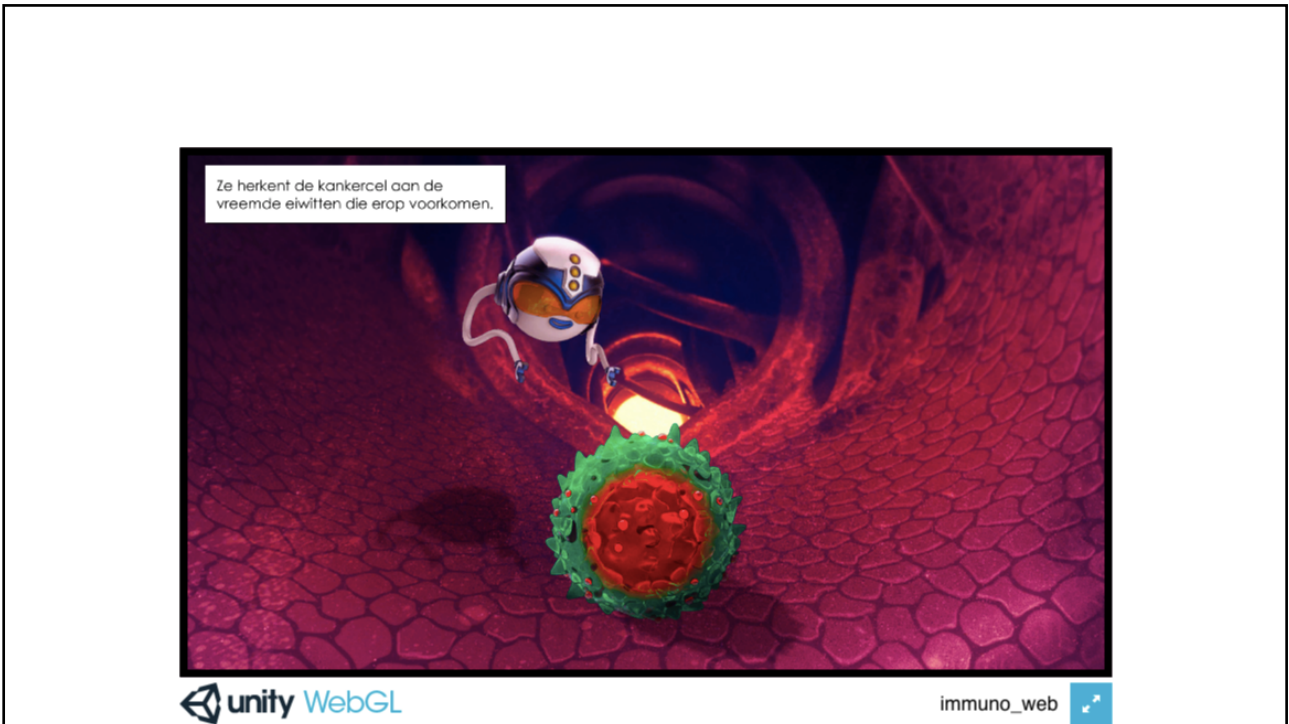
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De T-cel ontdekt een kankercel.

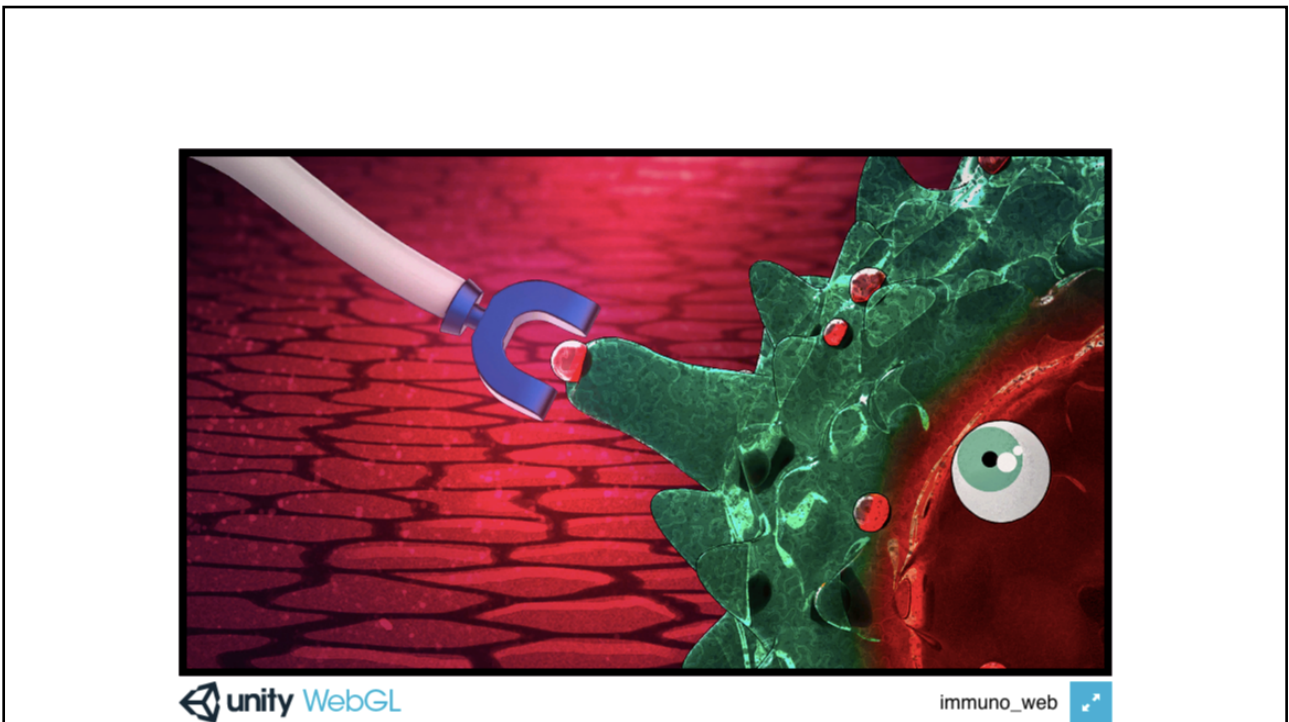
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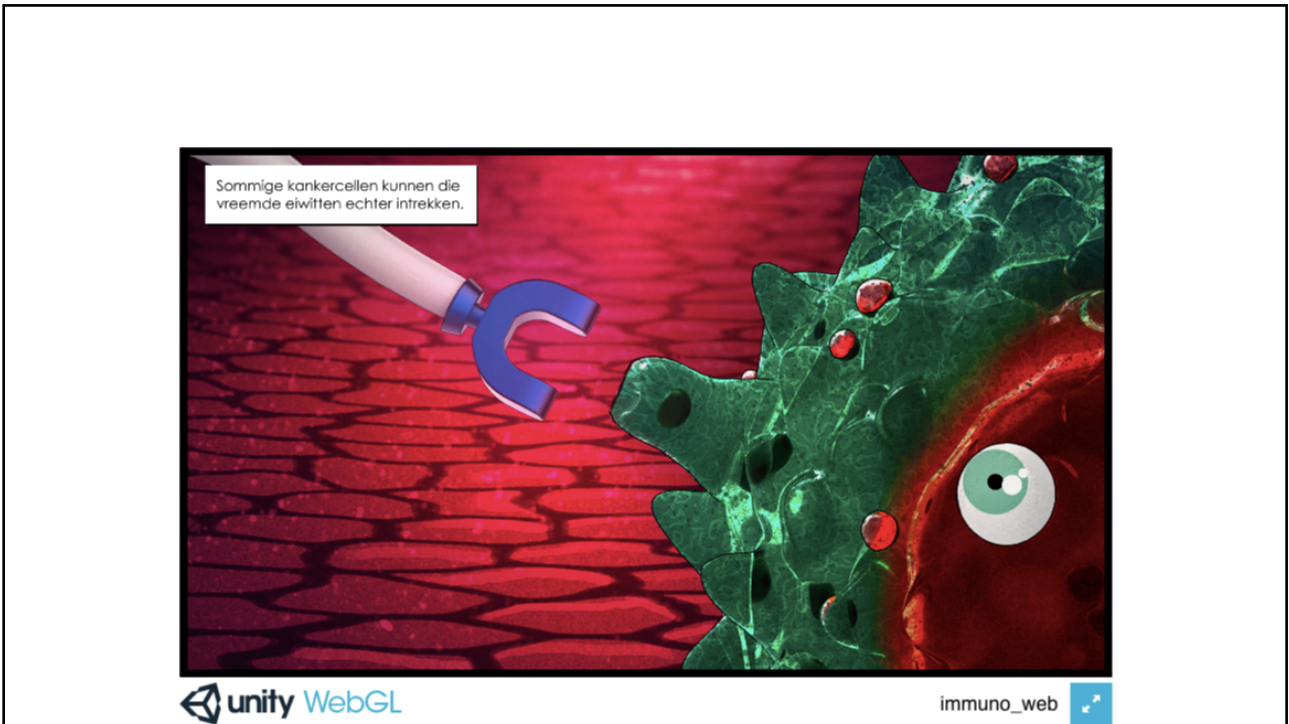
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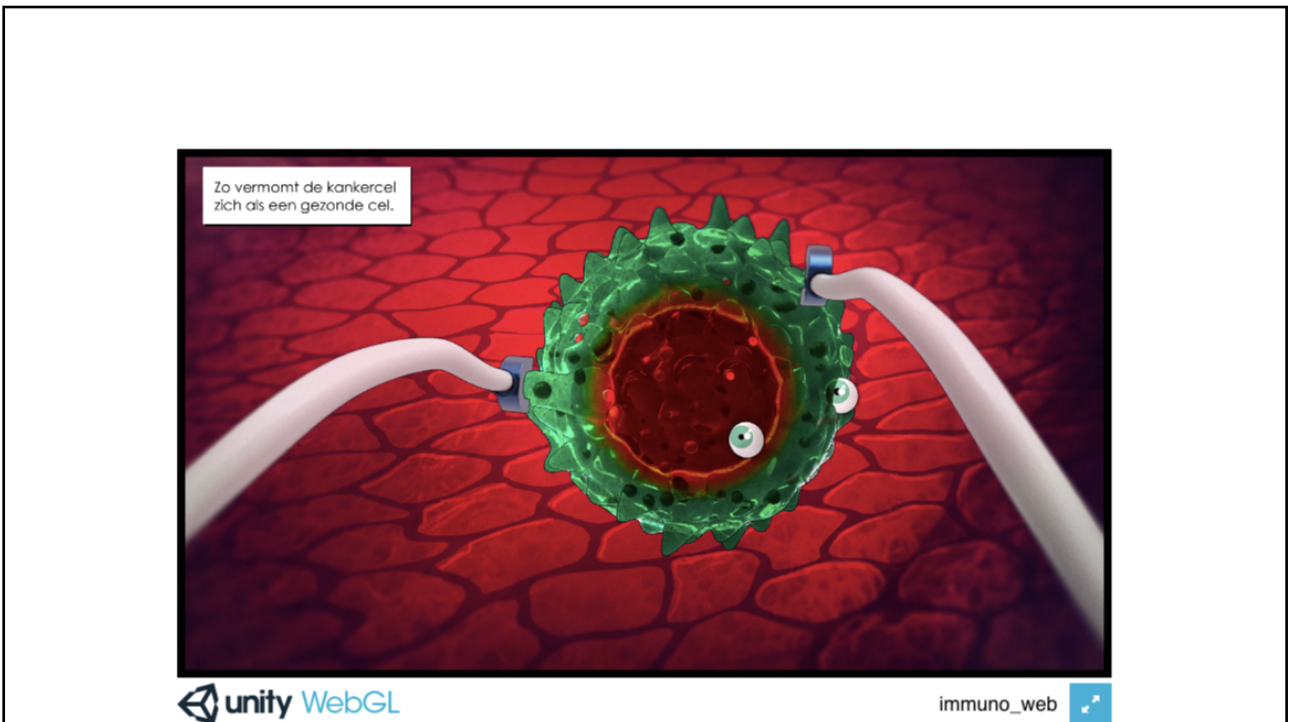
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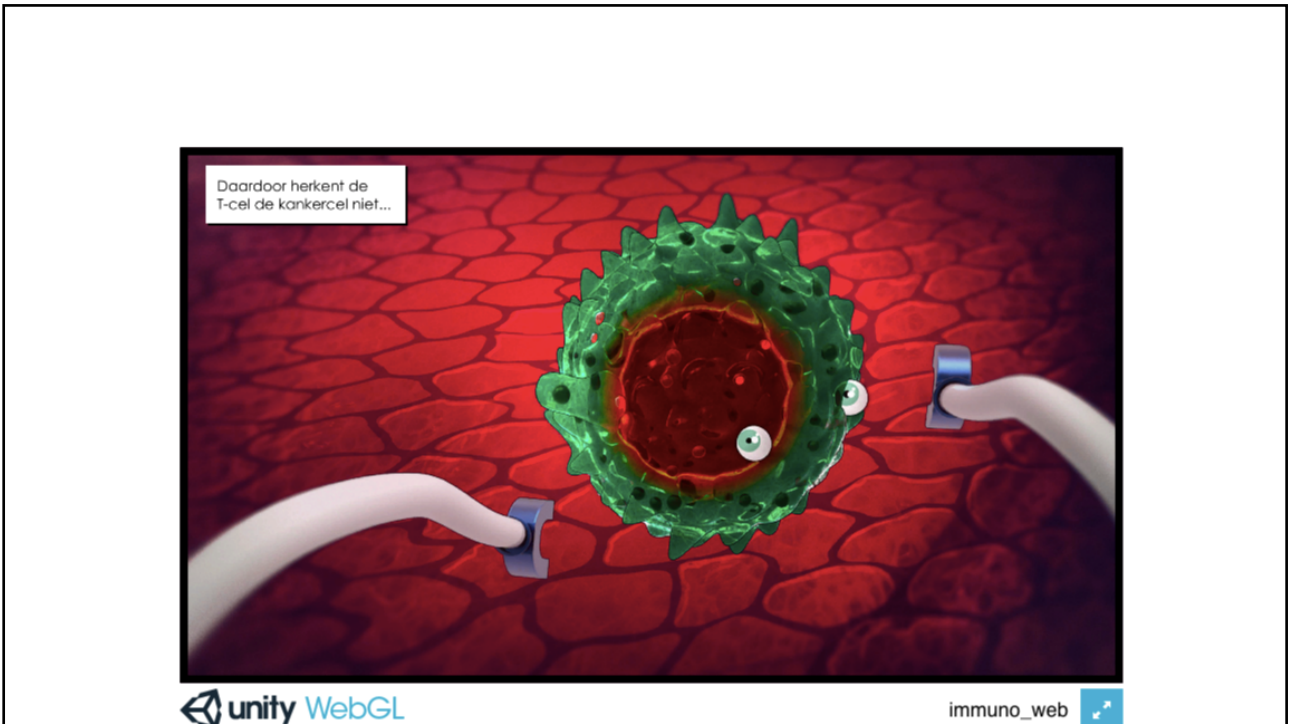
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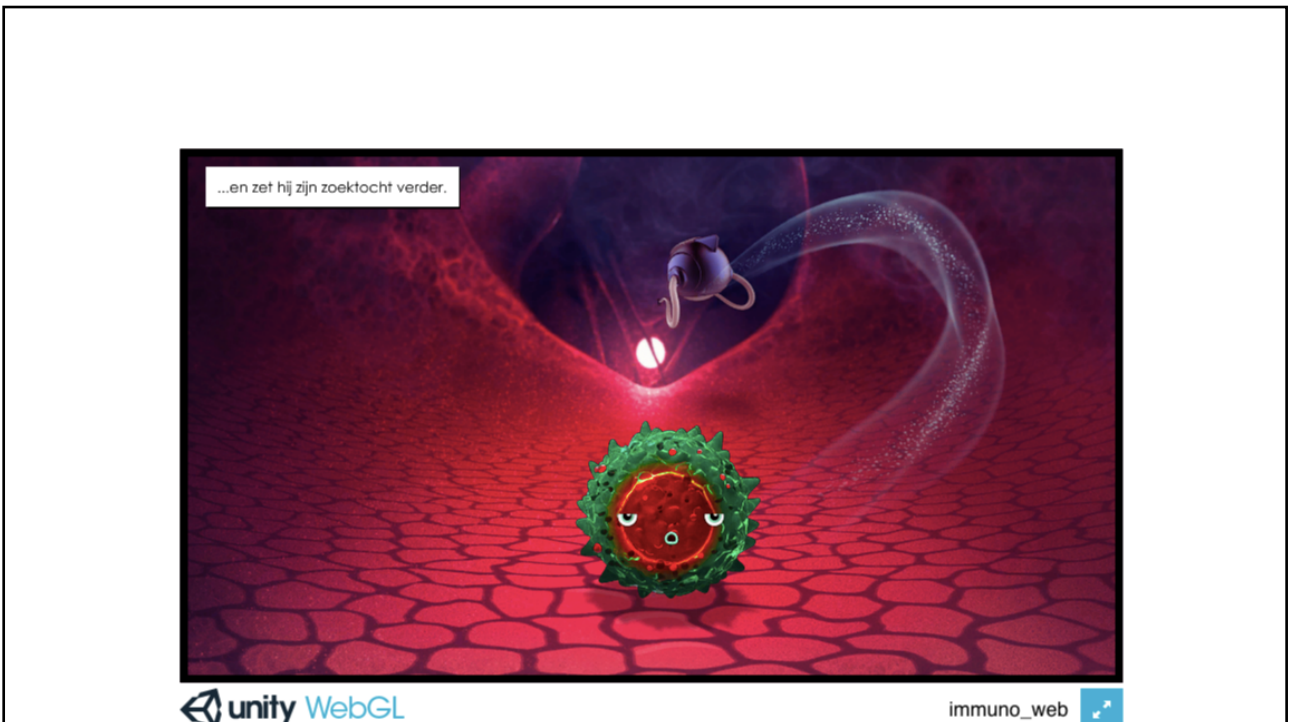
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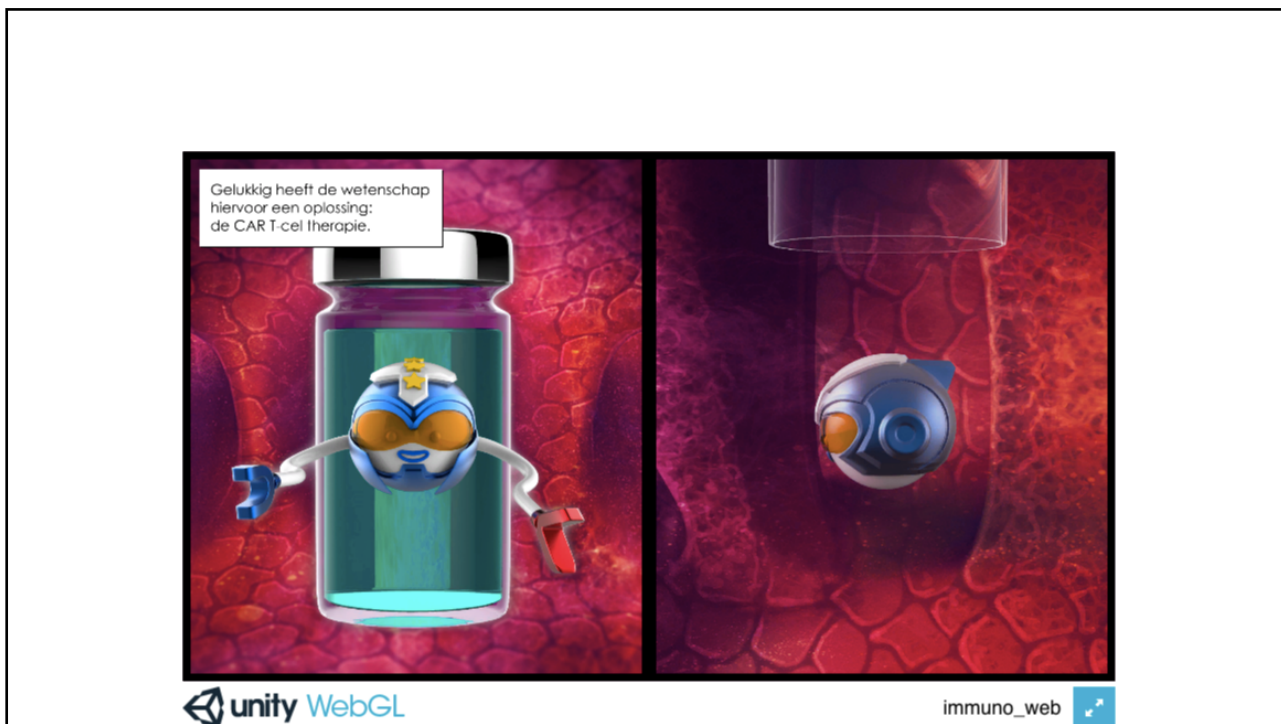
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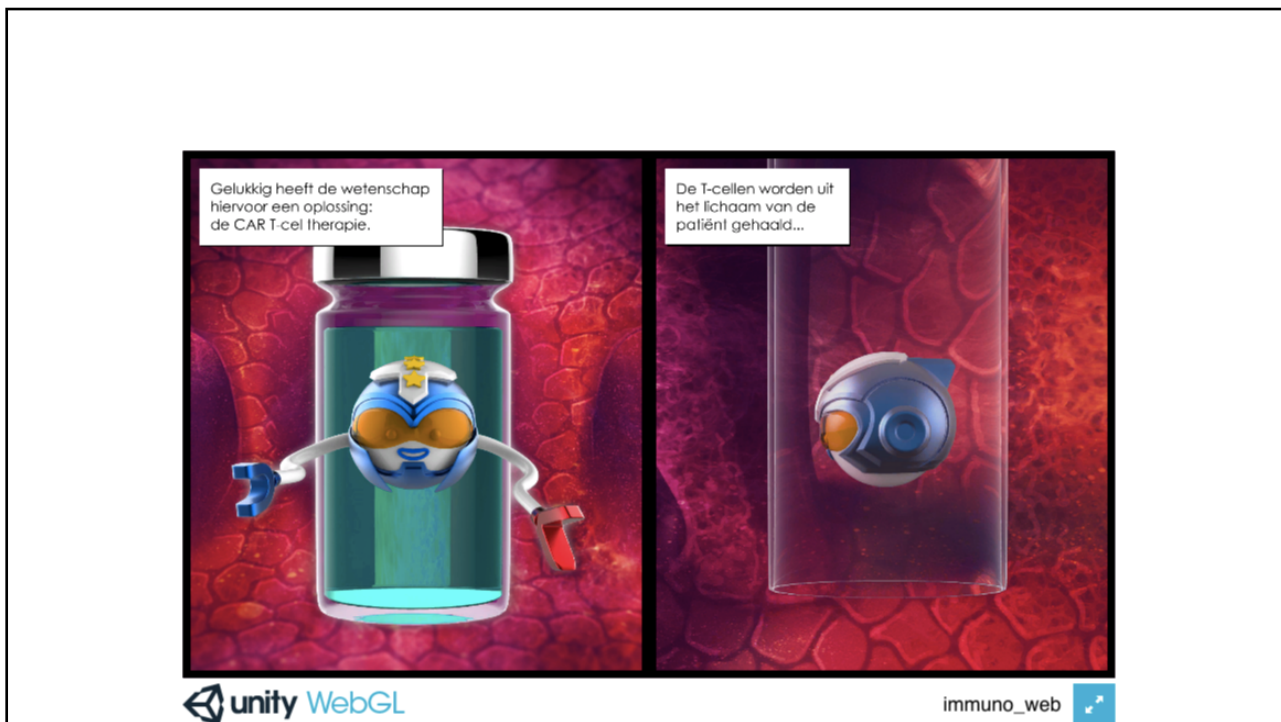
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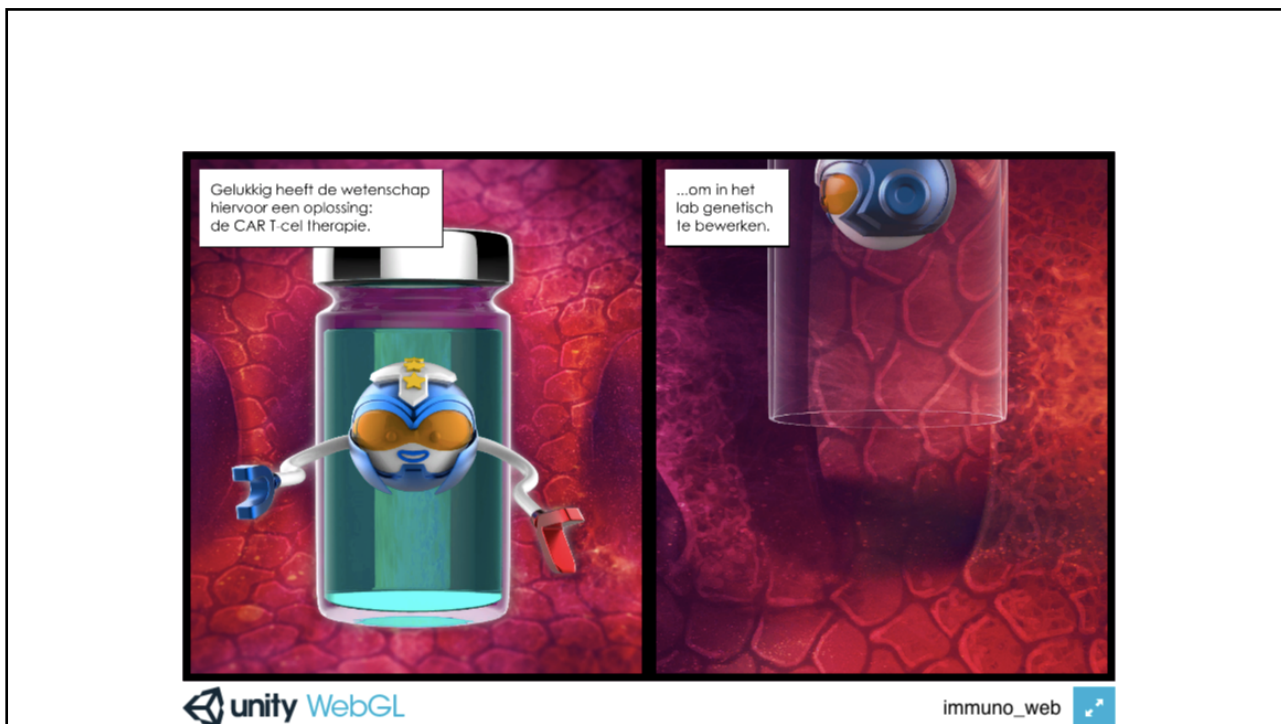
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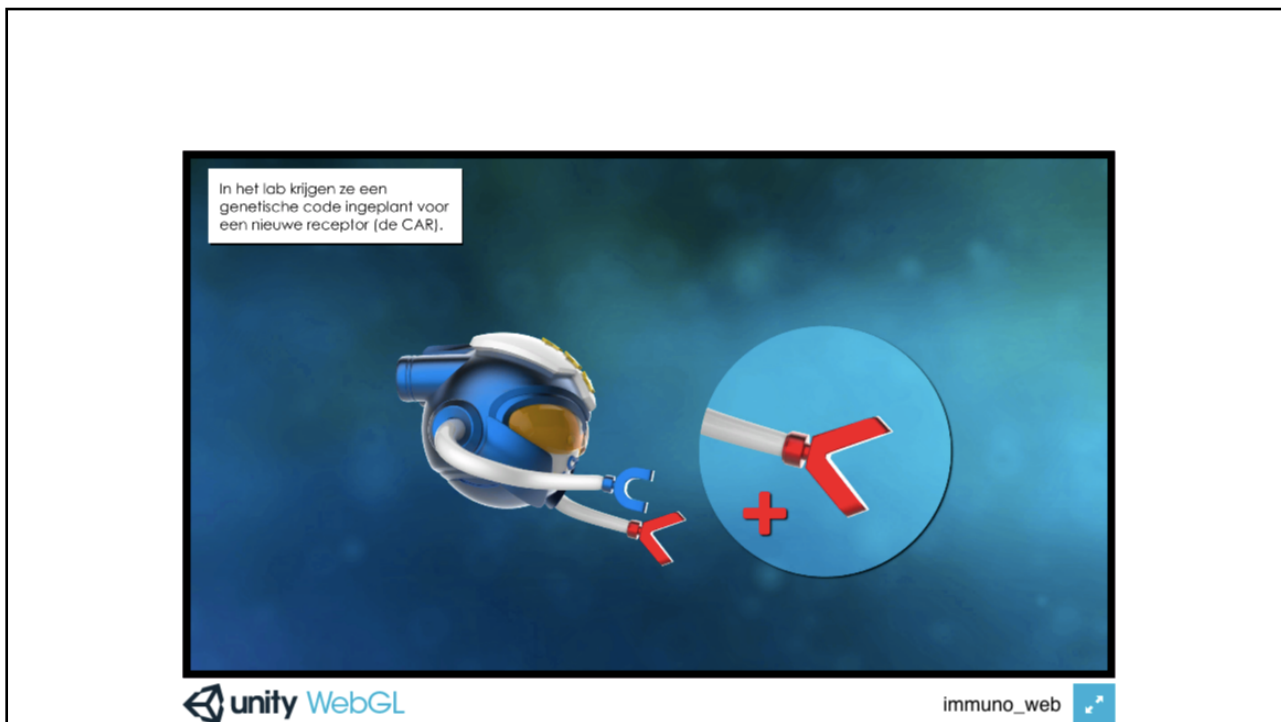
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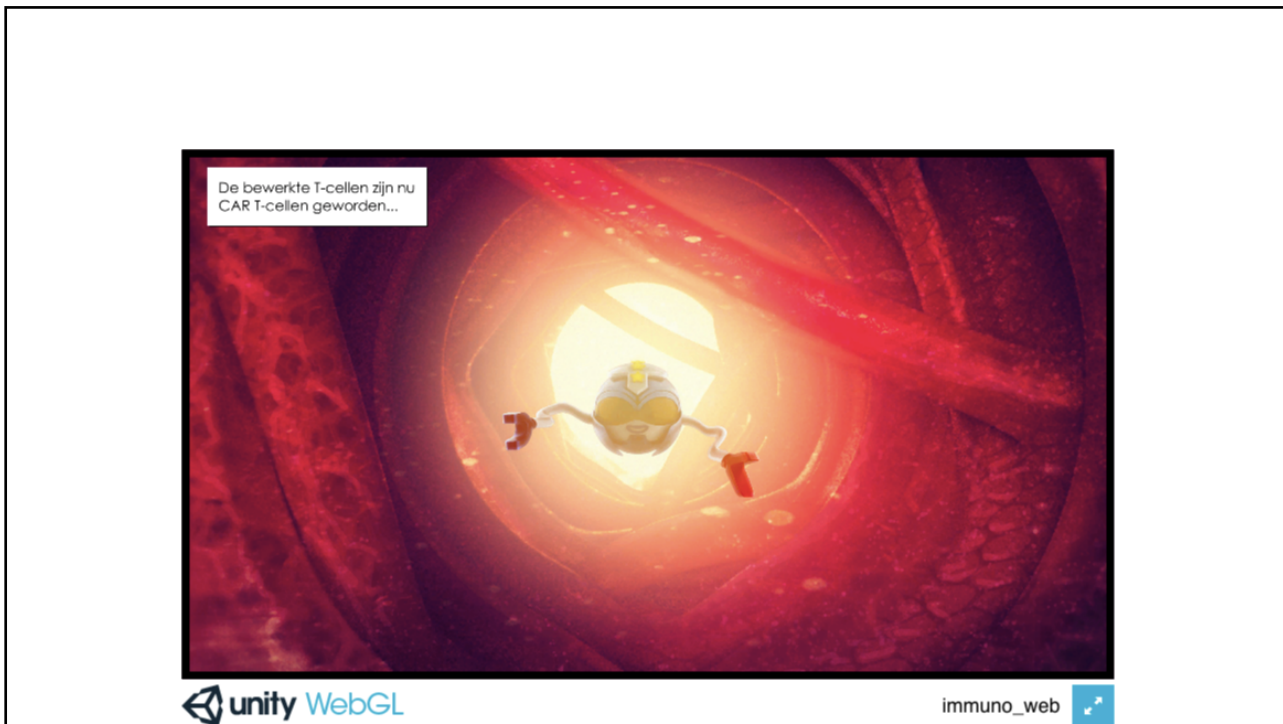
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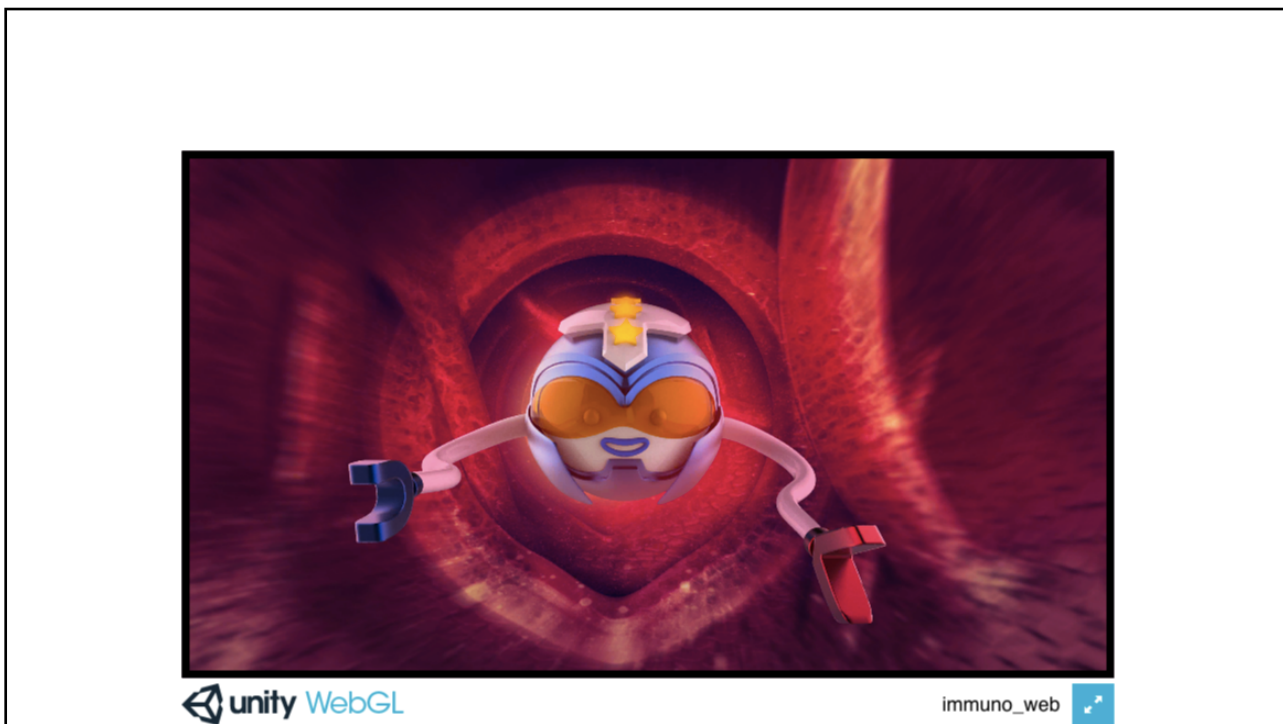
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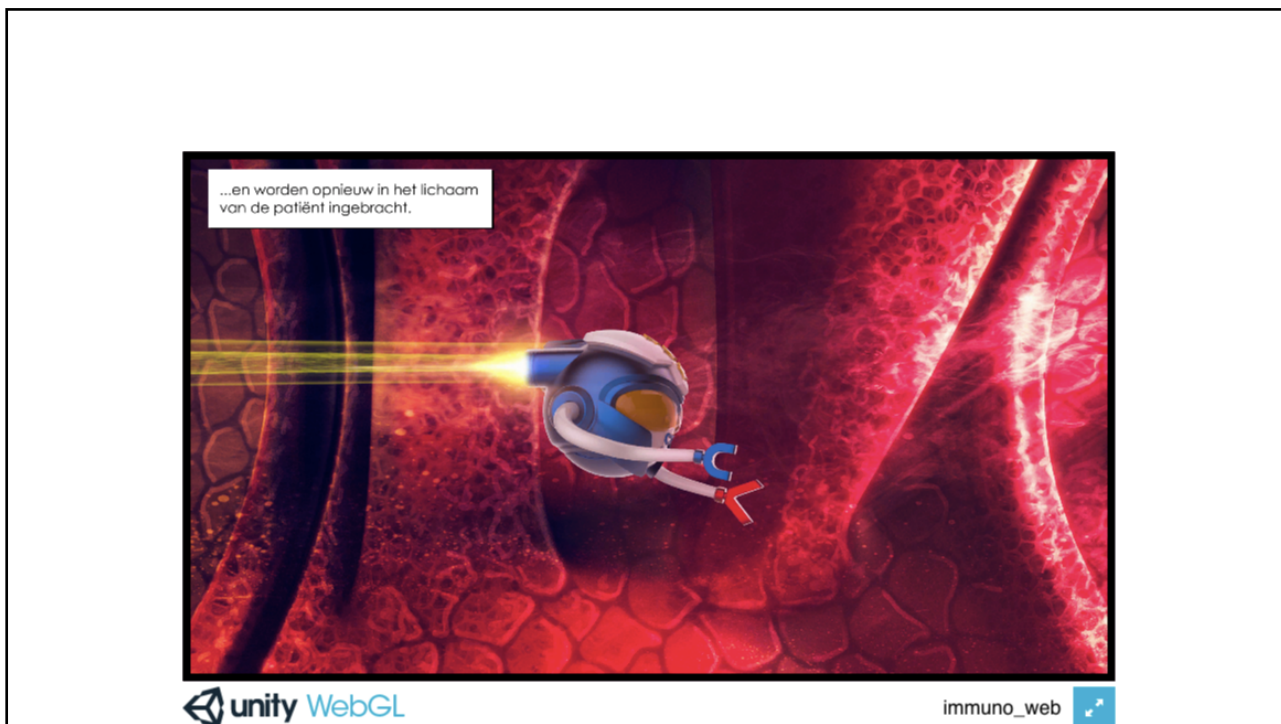
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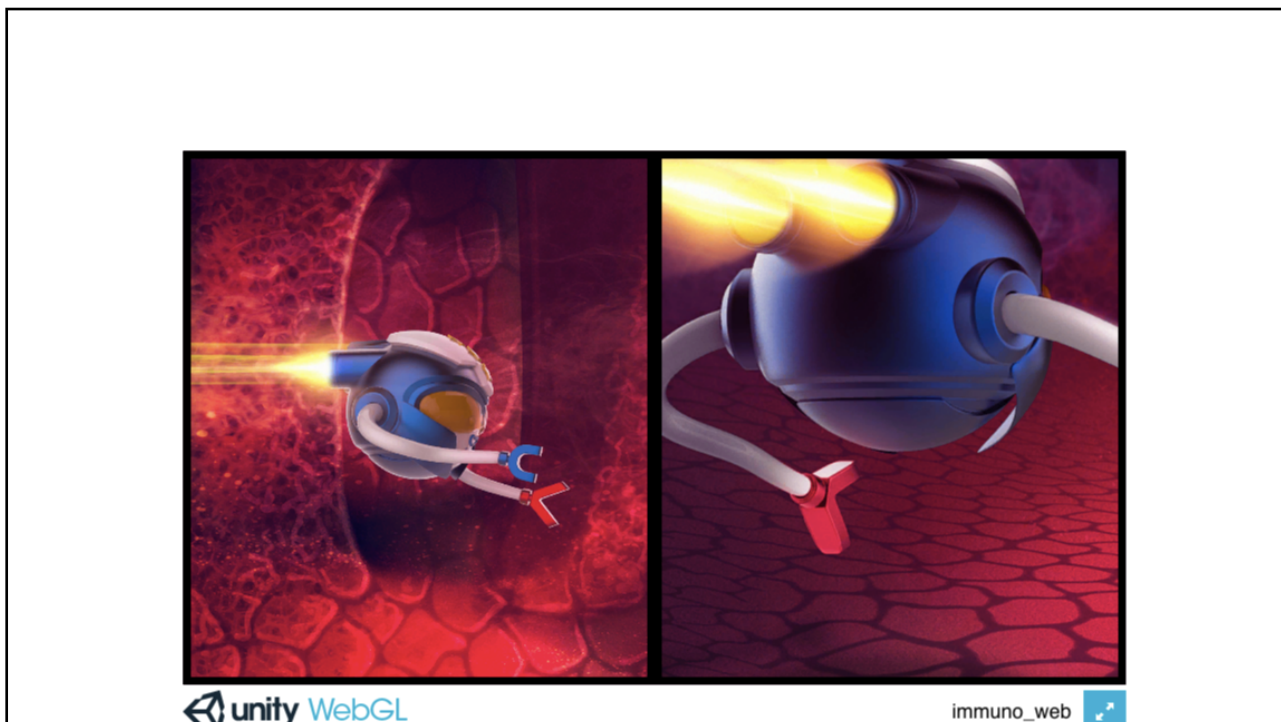
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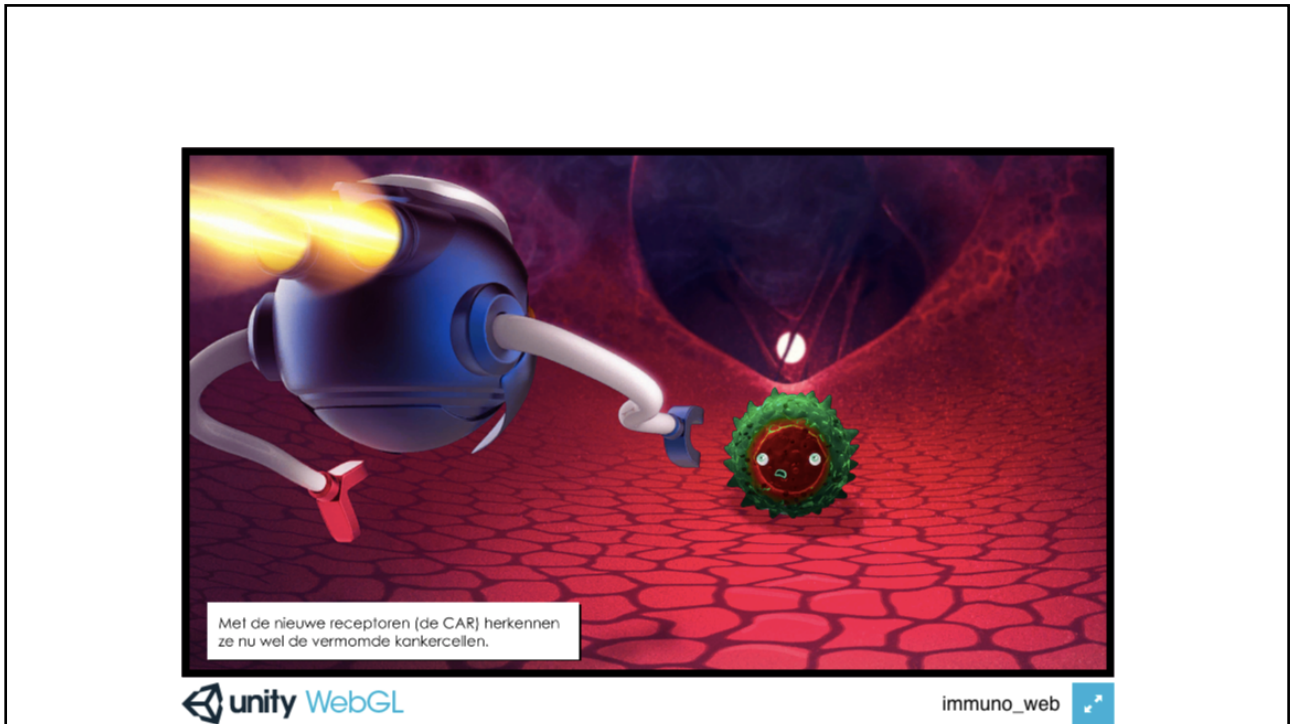
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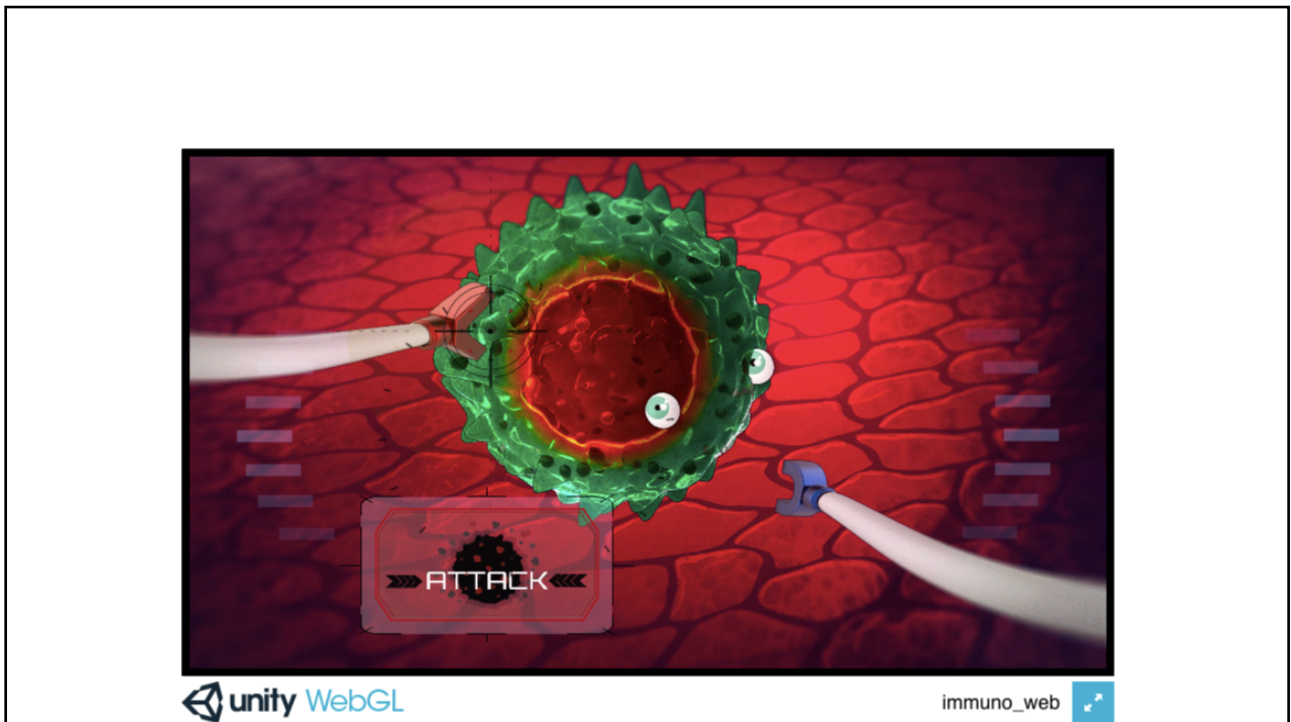
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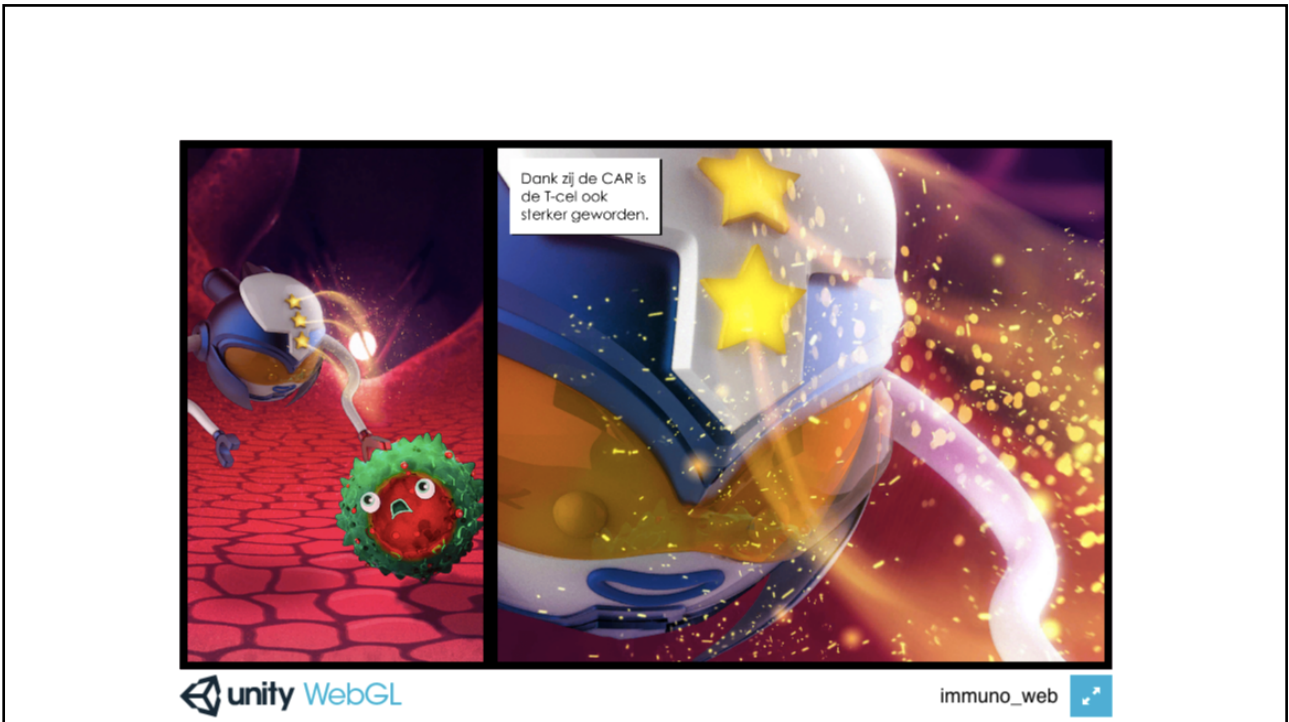
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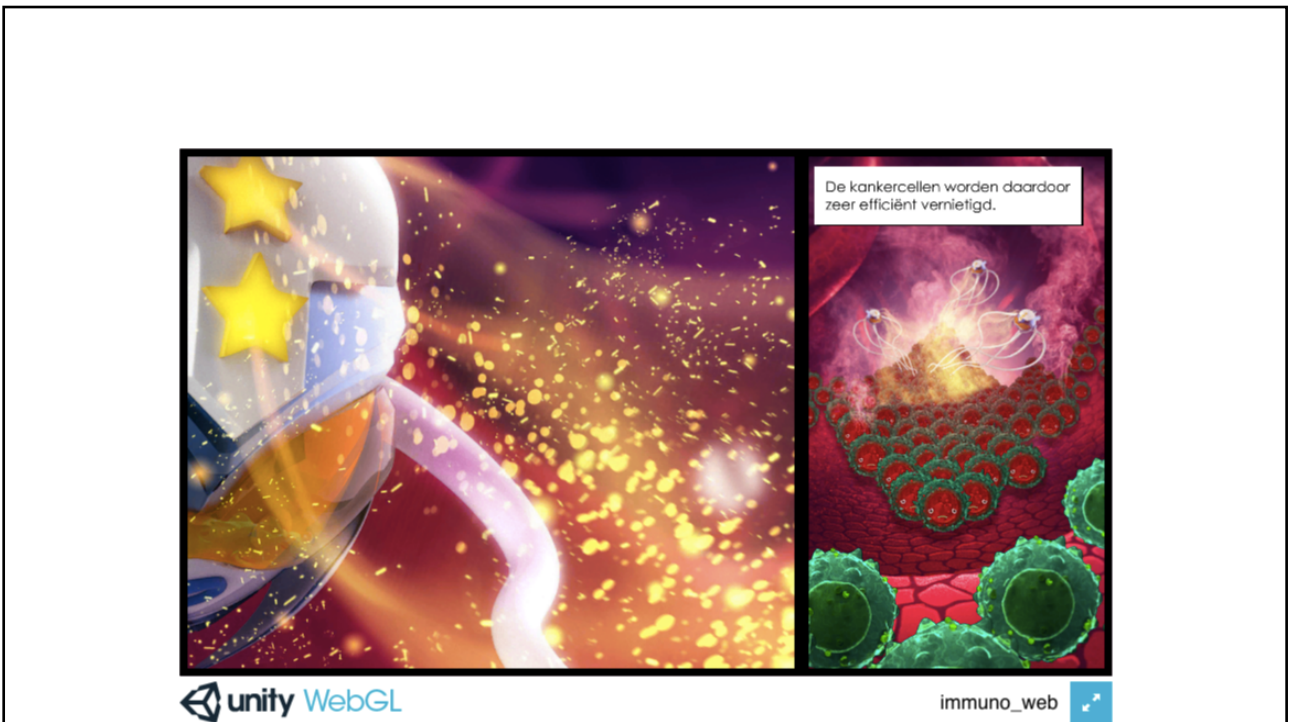
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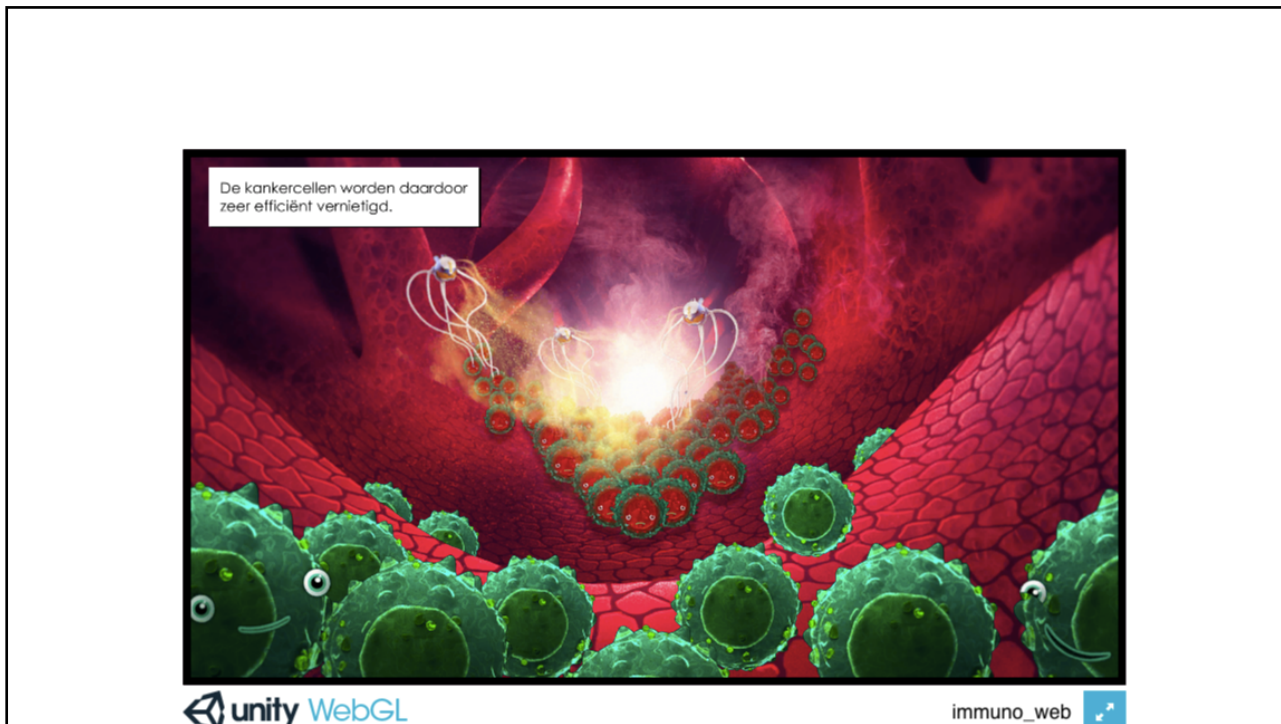
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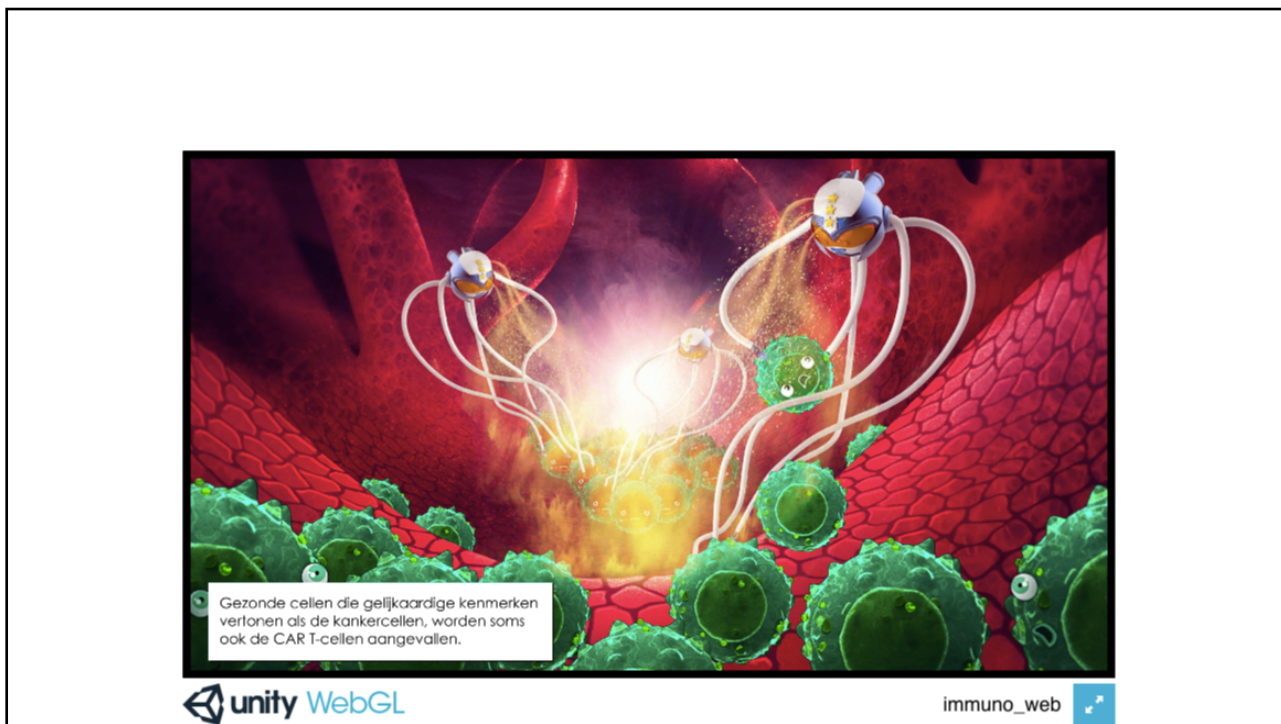
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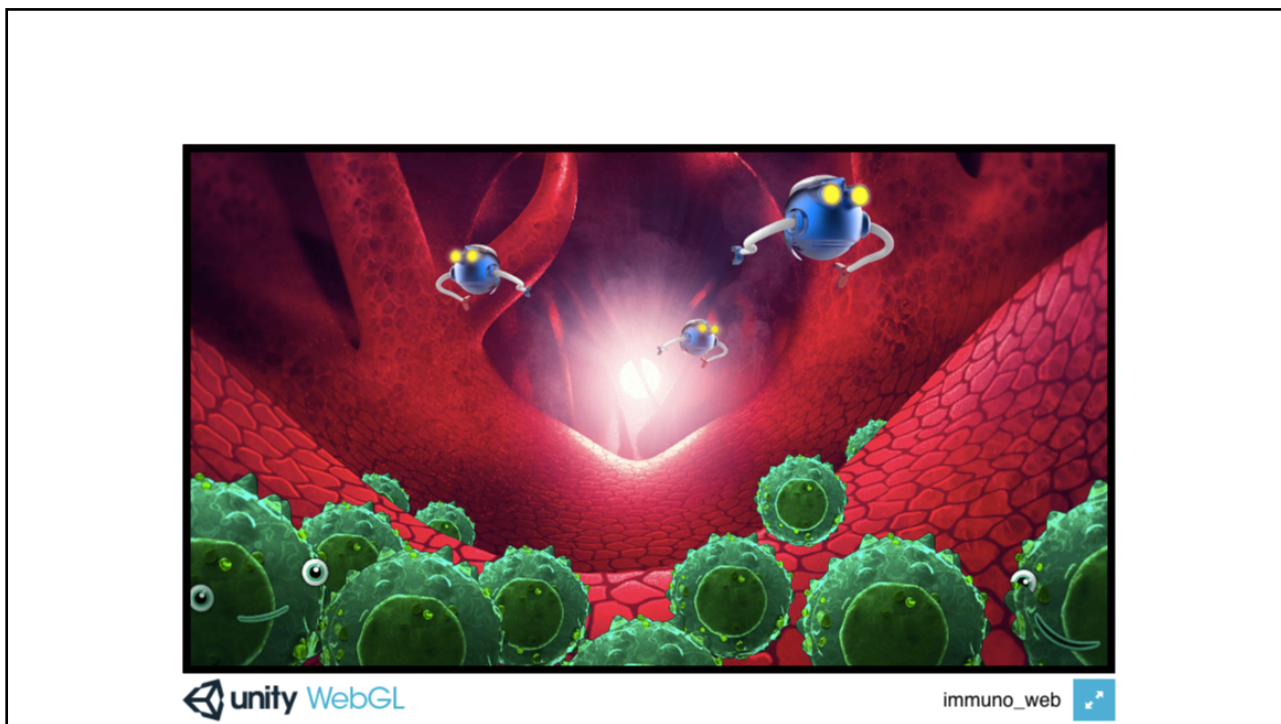
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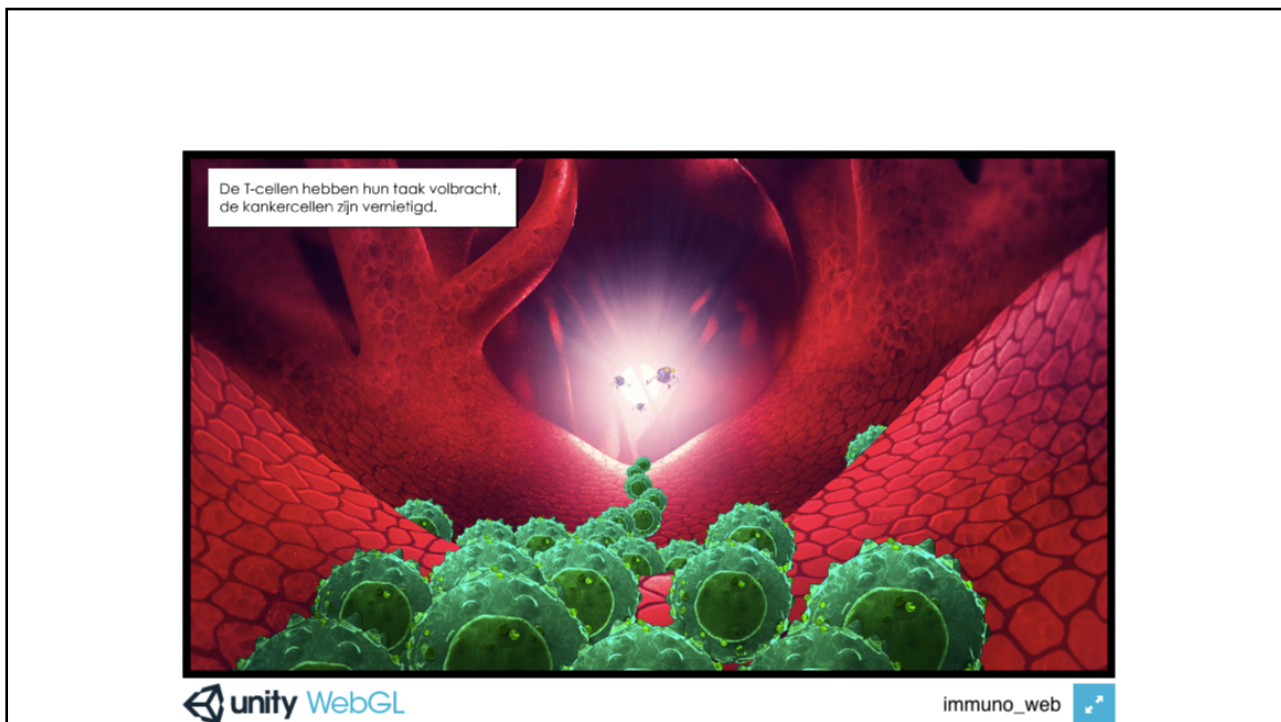
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CAR-T CEL THERAPIE

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CAR T-CEL THERAPIE

Emily



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CAR T-CEL THERAPIE

Emily



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CAR T-CEL THERAPIE

Emily

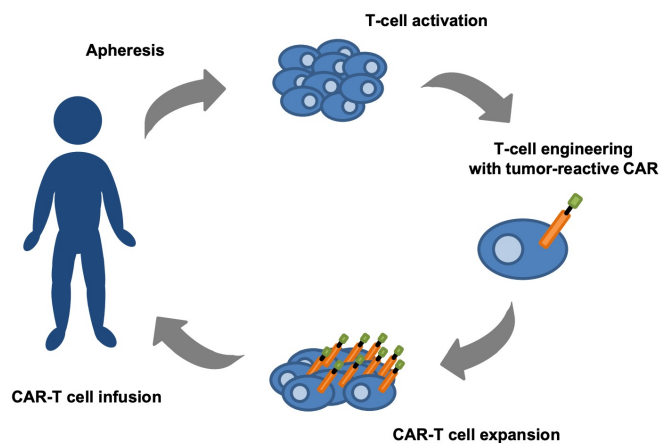


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CAR-T CEL THERAPIE



B Simon and U Uslu, *Exp Dermatology*, 2018

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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)



Het Nieuwsblad, 23/05/2019

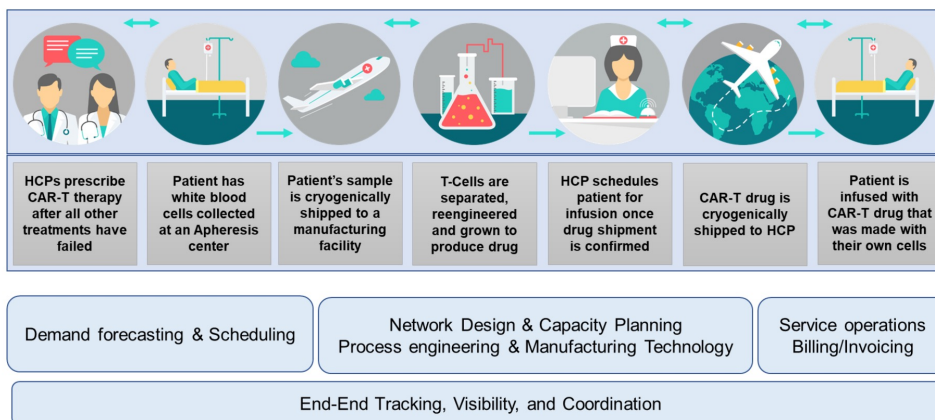


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UITDAGINGEN VOOR CAR-T THERAPIE

– Logistieke uitdagingen van een complex proces

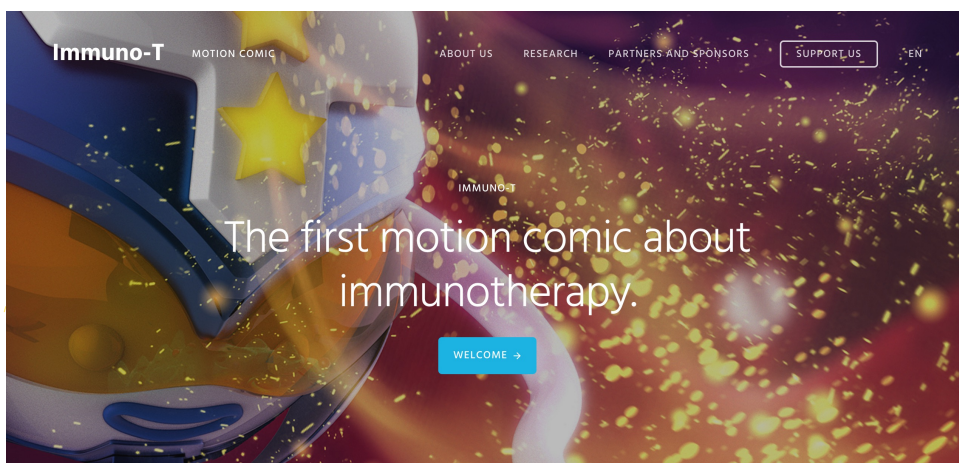


Shankar Suryanarayanan et al, Pharmexec.com

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CAR-T-CEL THERAPIE

– Patiënt educatie: immuno-T.inmotion.care

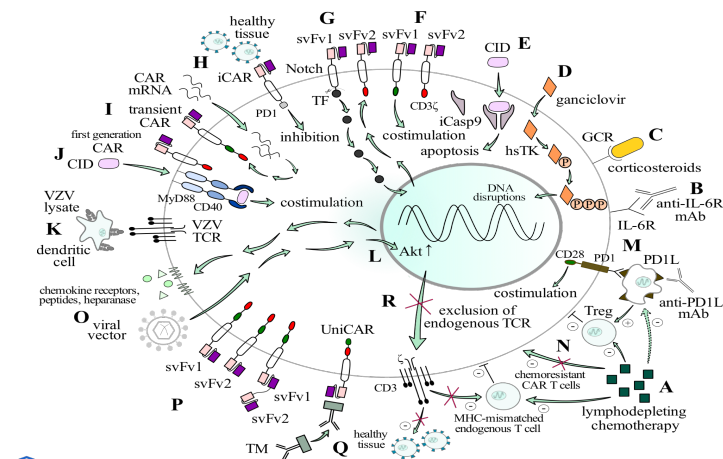


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CAR-T-CEL THERAPIE

– Nieuwe concepten in CAR-T design



Van Schandevyl S & Kerre T, Acta Clinica Belgica, 2019

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CAR-T-CEL THERAPIE

Wat brengt de toekomst?

- **Terugbetaling van eerste CAR-T therapie**
 - Wie kan deze extreem dure therapie krijgen?
 - Wie mag deze therapie toedienen?
 - Terugbetaling aferese - supportieve therapie – opname IZ – anti-IL6, enz...
- **Uitbreiding naar andere indicaties en ontwikkeling van steeds nieuwe CARs, universele CARs (off-the-shelf)**
- **Combinatie met andere therapie, zelfs andere immunotherapie**
- **Aanpak van vaste tumoren: TRUCKs**
- ...



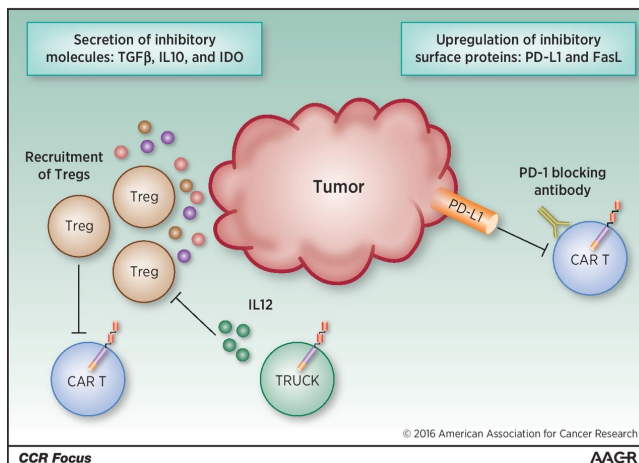
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CAR-T CEL THERAPIE VOOR VASTE TUMOREN

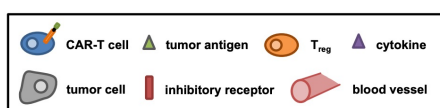
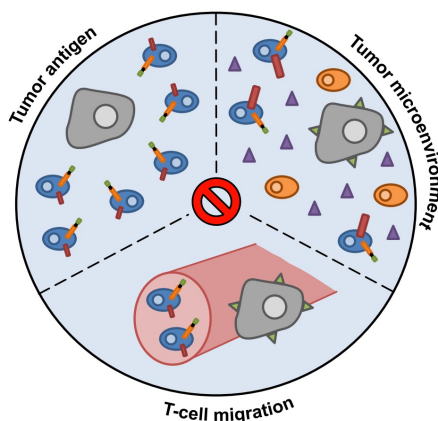
- Grotere uitdaging dan voor hematologische tumoren
 - Moeilijker doordringbaar
 - Micro-omgeving
 - Heterogeen

- Oplossing: TRUCKs!



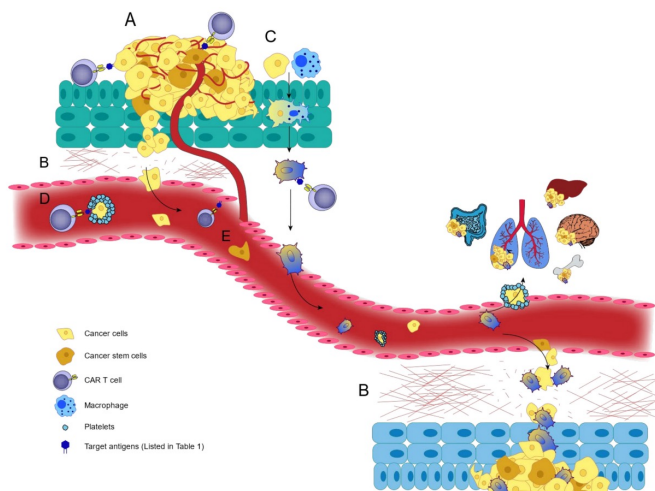
CAR-T-CEL THERAPIE VOOR MELANOOM?

- Uitdagingen voor CAR-T in melanoma



CAR-T-CEL THERAPIE VOOR MELANOOM?

– Melanoom: uitzaaiingen



T Soltantoyeh et al, Cells, 2021 71

CAR-T-CEL THERAPIE VOOR MELANOOM?

Cells 2021, 10, 1450

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Table 1. Surface molecules involved in melanoma metastasis, which could be targeted by CAR T cells.

Candidate Targets	Cellular Expression Pattern	CAR T Applicable to All Cancers?	CAR T Preclinical Study in Melanoma	CAR T Clinical Trial in Melanoma	
Angiogenic factors	VEGFR1	Endothelial cell	Yes [146]	-	
	VEGFR2	Endothelial cell	Yes [147]	-	
	VEGFR3	Endothelial cell	Yes [150]	+ [147-149]	NCT01218867
	FGFR1	Endothelial cell	No	-	-
	Neuropilin-1	Endothelial cell	No	-	-
	Neuropilin-2	Endothelial cell	No	-	-
	uPAR	Endothelial cell, Melanoma tumor cells	Yes [151]	-	-
Cadherins	CXCR1	Endothelial cell	No	-	
	CXCR2	Endothelial cell	No	-	
	avβ5	Endothelial cell	No	-	
Integrins	N-cadherin	Melanoma tumor cells	No	-	
	avβ3	Melanoma tumor cells	Yes [152]	+ [152]	
	avβ1	Melanoma tumor cells	No	-	
Adhesion molecules	α6β4	Melanoma tumor cells	No	-	
	MCAM/MUC18	Melanoma tumor cells	No	-	
	ALCAM/CD166	Melanoma tumor cells	Yes [153]	-	
	NCAM/CD56	Melanoma tumor cells	Yes [154]	-	
Ig Superfamily	L1-CAM	Melanoma tumor cells	Yes [155]	-	
	PECAM-1/CD31	Endothelial cell	No	-	
MMPs	MT1-MMP/MMP14	Endothelial cell, Melanoma tumor cells	No	-	
	ME7	Endothelial cell, Melanoma tumor cells	Yes [156]	-	
Leukocyte-cancer cell fusions	LAMP1/CD107a	MTFs	No	-	
	β1,6-branched oligosaccharides	MTFs	No	-	
	CD163	M2-macrophages, MTFs	No	-	
	CD204	M2-macrophages, MTFs	No	-	
	CD206	M2-macrophages, MTFs	No	-	
	CD44v3	Melanoma stem cells	No	-	
	MLANA/MART-1	MTFs, Melanoma tumor cells	No	-	
Embolic	PAR-1	Melanoma tumor cells	No	-	
	CD133	Melanoma stem cells	Yes [157]	-	
Cancer stem cells	CD20	Melanoma stem cells	Yes [158]	+ [159]	
	ARC5	Melanoma stem cells	No	-	
	CD271	Melanoma stem cells	No	-	
	ALDH1	Melanoma stem cells	No	-	
Chemotactic molecules	CXCR3	Melanoma tumor cells	No	-	
	ICF-1R	Melanoma tumor cells	Yes [160]	-	
	CXCR4	Melanoma tumor cells	No	-	
	CCR9	Melanoma tumor cells	No	-	

Abbreviations: MTFs: melanoma tumor fusion cells.

CAR-T-CEL THERAPIE VOOR MELANOOM?

– Doelwitten voor CAR-T in melanoom

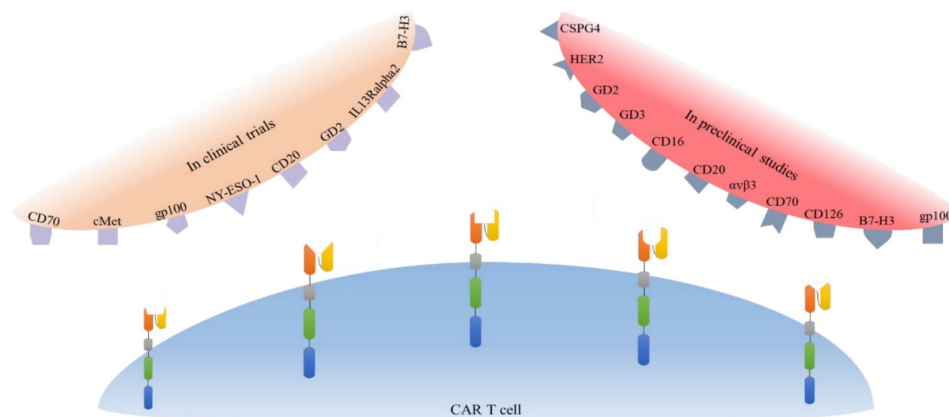


Figure 2. Schematic overview of target antigens for CAR T cells in the pre-clinical and clinical studies. To date, these antigens have been considered as potential targets for CAR T cells in pre-clinical studies and in clinical trials in melanoma patients.

T Soltantoyeh et al, Cells, 2021

CAR-T-CEL THERAPIE VOOR MELANOOM?

– Doelwitten voor CAR-T in melanoom: preklinisch

Study	Model of Study and Design	Target Tumor Antigen	Findings
[161]	A375 melanoma cell line CD16-CAR T + CD20 and MCSP antibodies NOG mice	CD16	Increased cytotoxic activity against target cells
[162]	HER2 ⁺ melanoma cells HER2 CAR T cells	HER2	Her2 ⁺ melanoma cell killing in vitro and in vivo
[163]	624-mel metastatic melanoma cell line CD126 CAR T cells SCID Beige mice	CD126	Increased cytotoxic activity against CD126 ⁺ melanoma cells
[165]	HLA-A2-positive Malm-3m cells GPA7-28c transduced T cells or un-transduced T cells	GP100-HLA-A2 complex	Enhanced cytotoxicity against melanoma cells in vitro Rapid tumor regression, delayed tumor growth and enhanced survival in vivo
[149]	B16 melanoma mice: Anti-VEGFR-2 CAR T-cells and T cells specific for tumor antigens (gp100, TRP-1, TRP-2)	VEGFR-2	Improved tumor-free survival and enhanced infiltration and persistence of CAR T cells
[148]	C57BL/6 mice B16BL6 cell lines VEGFR-2 CAR-T cells		mRNA Electro-porated CAR-T cells showed similar tumor killing, cytokine production and cytotoxic activity compared to conventional CAR T cells
[159]	primary and metastatic cutaneous melanoma Tumor cells MCSF or CD20 CAR T cells	CD20 & MCSF	Efficient elimination of melanoma cells co-expressing CD20 and MCSF in vivo
[166]	Rag ^{-/-} cy ^{-/-} mice MCSF ⁺ Melan cells CEA CAR T or MCSF CAR T cells	MCSF	Increase survival of mice receiving first & 2nd generation CAR-T cells
[167]	T2.A1; Mel526; A375M cell lines MCSF-specific CAR T cells		Safer activity, similar cytotoxicity and reduced cytokine production of γ/δ engineered T cells against melanoma cells compared to conventional CAR T cells
[169]	CSPG4 (MCSF) specific CAR T cells, gp100 specific TCR α/β T cells or T cells expressing both receptors (TETARs)	gp100 and MCSF	Similar melanoma tumor cell killing capacity, reduced unpecific response and recognition of both antigens by TETARs
[176]	SK-Mel-28 melanoma cell lines anti-GD2 ICAR T cells + Pembrolizumab (PD-1 inhibitor)	GD2	Melanoma cell killing in vitro
[171]	SCID-Luc mice 4405M or P1143 cell lines NT or GD2 CAR T cells	GD2	Significant anti-tumor activity of GD2 CAR T cells both in vitro and in vivo
[170]	BALB/c nude mice GD3 ⁺ M21 cell lines GD2CAR T cells	GD3	Enhanced cytotoxicity, proliferation, and cytokine production of ScFv-CD28/TCRC receptor expressing T cells
[172]	NSG mice A375-FLuc cell line B7-H3 CAR T cells	B7-H3	Enhanced survival and significant anti-tumor activity of B7-H3 CAR T cells against Melanoma cells
[164]	NSG mice NCI-H460 or A375 cell lines CD70 CAR2, or B7-H3 CAR T-cells	CD70 & B7-H3	Reduction of tumor burden Increased the overall survival of the mice

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CAR-T-CEL THERAPIE VOOR MELANOOM?

– Doelwitten voor CAR-T in melanoom: klinisch

Table 3. Summary of clinical trials evaluating CAR T cell-based treatment for melanoma.

Study	Year of Study	Population and Design	Target Tumor Antigen	Overall Result
NCT01218867 [177]	Started in 2010. Last results update in 2019.	Phase I/II: 24 patients with metastatic cancer, metastatic melanoma, and renal cancer. Cyclophosphamide, Aldesleukin, Fludarabine, and different doses of anti-VEGFR2 CAR T cells (CD8 plus PBL)	VEGFR2	Terminated due to no objective response. 23/24 (95.8%) had progressive and 1/24 (4.1%) had a stable disease. 23/24 (95.8%) had serious or non-serious adverse events. 5/24 (20.8%) had serious adverse events; 3/5 (60%) had increased ALT, AST, and bilirubin; 2/5 (40%) had hypoxia; 1/5 (20%) had pain, infection, nausea, and vomiting.
NCT02107963 [2]	Started in 2014	Phase I: Up to 36 children and young adults with GD2+ solid tumors (melanoma, sarcoma, osteosarcoma, and neuroblastoma). Cyclophosphamide, AP1903, anti-GD2 CAR T cells	GD2	Completed but no published results.
NCT03635632 [7]	Started in 2019	Phase I: 94 patients with several GD2+ malignancies including Uveal Melanoma. Receiving: Cyclophosphamide, Fludarabine, and CPR-GD2 CAR T cells.	GD2	Recruiting patients. C7R gene is added to increase the CAR T cell's survival and provide a constant cytokine supply.
NCT03060356 [1]	Started in 2016	Early phase I: 77 patients with malignant melanoma or breast cancer receiving RNA anti-cMET CAR T cell	cMet	Terminated (halt in funding). No results published.
NCT02830724 [178]	Started in 2017	Phase I/II: Adults with five types of CD70-expressing cancers including melanoma. Cyclophosphamide, Fludarabine, Aldesleukin, and anti-hCD70 CAR-transduced PBL.	hCD70	Suspended. No study results published.
NCT03649529 [179]	Started in 2018	Early phase I: 6 patients with malignant melanoma receiving GPA-TrIMAR CAR T cells	gp100	Recruiting patients.
NCT03638206 [5]	Started in 2018	Phase I/II: 73 patients with ten types of cancers including melanoma. Different CAR T/TCR-T regimens, including anti-NY-ESO-1 for melanoma	NY-ESO-1	Recruiting patients.
NCT03893019 [180]	Started in 2019	Early Phase I: 15 patients with CD20+ unresectable stage III or IV melanoma. anti-CD20 CAR T cells (NB-CAR22.1)	CD20	Recruiting patients.
NCT04119024 [6]	Started in 2019	Phase I: 24 patients with stage IIIC and IV Melanoma. Receiving: Cyclophosphamide, Fludarabine Phosphate, Recombinant Interleukin-2, and IL13Ralpha2-specific Hinge-optimized 4-1BB-co-stimulatory CAR/Truncated CD19-expressing Autologous naive and memory T Cells.	IL13Ralpha2	Recruiting patients.
NCT04483778 [181]	Started in 2020	Phase I: 68 children and young adolescents with several recurrent/refractory malignancies, including melanoma. Receiving: Arm A: second-generation 4-1BB, B713-EGFR-DHFR CAR T cells Arm B: second-generation 4-1BB, B713-EGFR-DHFR (selected) and a second-generation 4-1BB, CD19-Her2G CAR T cells	A: B713 and B: Bispecific B713/CD19	Recruiting patients.

Abbreviations: PBL: Peripheral blood lymphocytes, VEGFR2: Vascular Endothelial Growth Factor Receptor-2.



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