ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

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ION immuno-oncology network Ghent

Immunotherapy in Hematology

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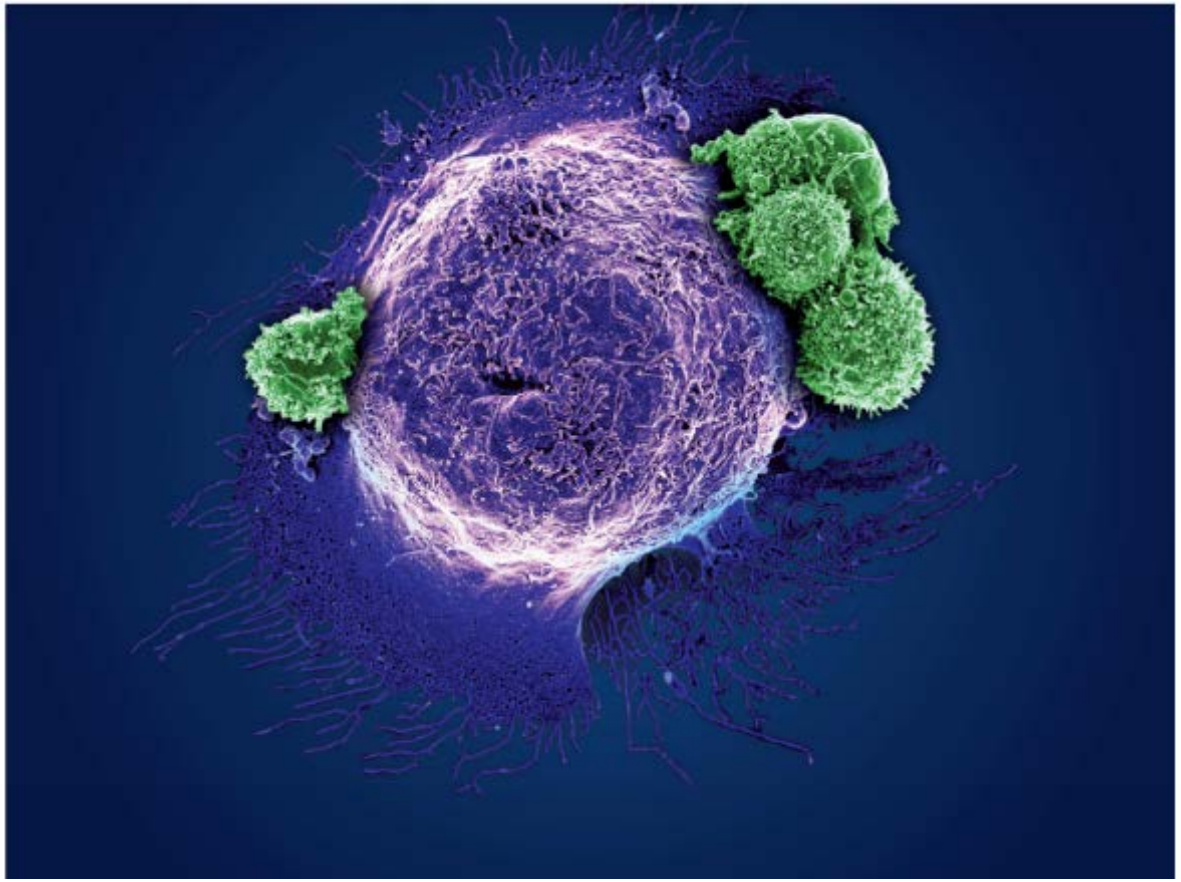
Emily's story

Emily’s story

Emily’s story

Emily Whitehead

Immunotherapy



Immunotherapy: overview

Active immunotherapy

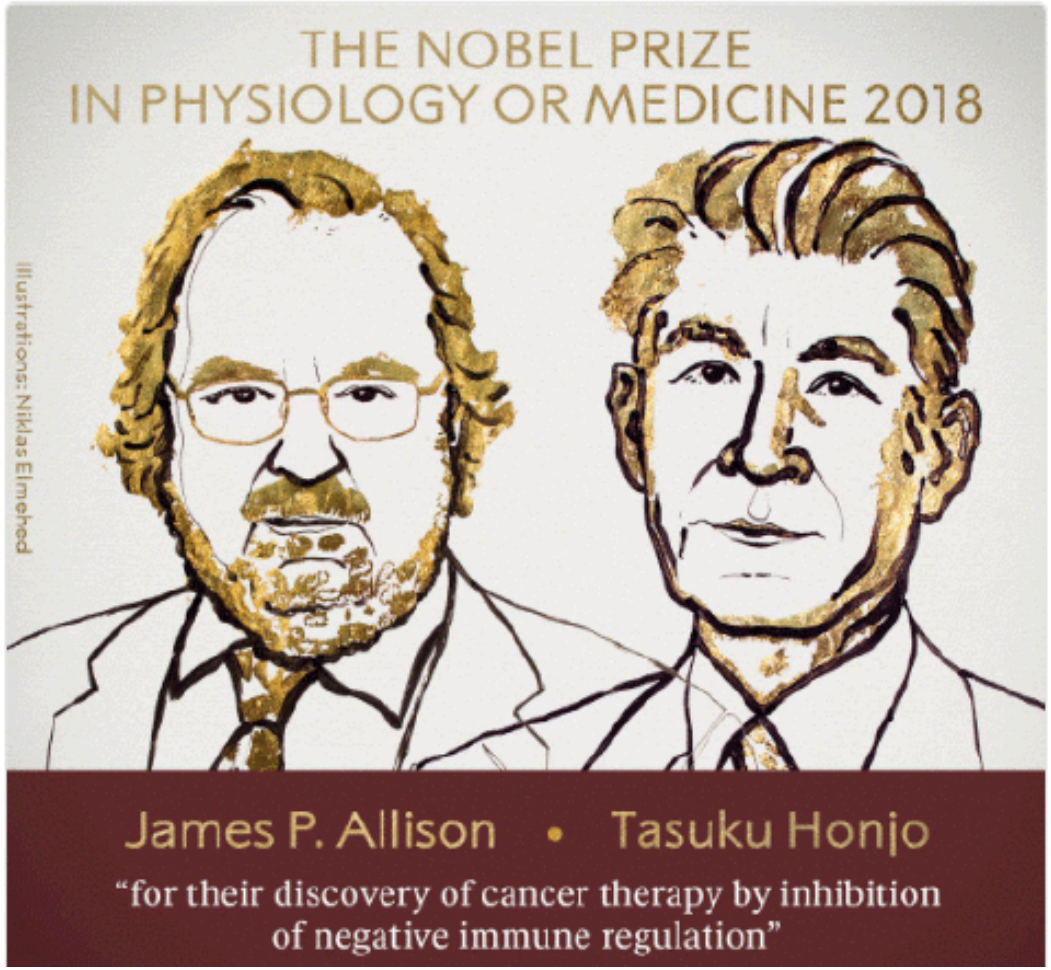
- Vaccination
- Cytokines
- Modulatory immunotherapy: checkpoint inhibitors

Passive immunotherapy

- Monoclonal antibodies
- Allogeneic stem cell transplantation
- T cell therapy
  - TIL/PBL
  - TCR/CAR transduction of circulating T cells
  - Antigen specific T cells from stem cells

CAR, chimeric antigen receptor; PBL, peripheral blood lymphocytes; TCR, T cell receptor; TIL, tumour infiltrating lymphocytes.
Galluzi et al. Oncotarget. 2014;5:24:12472–508.

Checkpoint inhibitors



Checkpoint inhibitors in hematology

- Reimbursed in Belgium for relapsed Hodgkin's lymphoma
- Conflicting results in clinical trials for multiple myeloma (toxicities)
- Under evaluation in clinical trials for various cancers, including:
  - Multiple myeloma, T-NHL, DLBCL, AML, and MDS
  - Combination of checkpoint inhibitors and …

AML, acute myeloid leukaemia; DLBCL, diffuse large B-cell lymphoma; MDS, Myelodysplastic syndromes; T-NHL, T-cell non-Hodgkin lymphoma.

Checkpoint inhibitors in hematology

Table 1 Notable ongoing clinical trials in hematological malignancies

Malignancies	Clinical trial #	Phase	Drug	Study description	Other name
Lymphoid neoplasm	NCT02181738	2	Nivolumab	Clinical activity of anti-PD-1 antibody in R/R CHL patients	CheckMate 205
	NCT01953692	2	Pembrolizumab	Clinical activity of anti-PD-1 antibody in R/R CHL patients	KEYNOTE-013
	NCT02857426	2	Nivolumab	Anti-PD-1 antibody in R/R PCNSL and PTL	
	NCT02576990	2	Pembrolizumab	Anti-PD-1 antibody in R/R PMBL	KEYNOTE-170
	NCT02220842	1	Atezolizumab	Anti-PD-L1 antibody in combination with anti-CD20 antibody to R/R DLBCL or FL	
Plasma cell neoplasm	NCT02036502	1	Pembrolizumab	Clinical activity of anti-PD-1, lenalidomide and low-dose dexamethasone in R/R PCM patients shown	KEYNOTE-023
	NCT02903381	2	Nivolumab	Lenalidomide, low-dose dexamethasone and anti-PD-1 antibody in smoldering PCM patients	
	NCT01592370	1	Nivolumab	Clinical activity of anti-PD-1 antibody in R/R PCM patients	
	NCT02726581	3	Nivolumab	Pomalidomide and dexamethasone with or without anti-PD-1 antibody in R/R PCM patients	CheckMate 602
	NCT02579863	3	Pembrolizumab	Pomalidomide and dexamethasone with or without anti-PD-1 antibody in treatment-naïve PCM patients	KEYNOTE-185
Myeloid neoplasms	NCT02530463	2	Nivolumab	HMA, ipilimumab, and anti-PD-1 antibody in MDS patients	
	NCT01953692	1	Pembrolizumab	Anti-PD-1 antibody in HMA-failed MDS patients	
	NCT02845297	2	Pembrolizumab	Anti-PD-1 with HMA in R/R AML patients	
	NCT02275533	2	Nivolumab	Anti-PD-1 antibody as post-remission therapy in AML patients	
	NCT02117219	1	Durvalumab	Anti-PD-L1 antibody, HMA, and tremelimumab in MDS patients	

R/R relapsed refractory, *PCNSL* primary central nervous system lymphoma, *PTL* primary testicular lymphoma, *PMBL* primary mediastinal large B cell lymphoma, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *PCM* plasma cell myeloma, *HMA* hypomethylating agent, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukemia

Chi Young Ok and Ken H. Young, J Haematol & Oncol, 2017

Immune-related adverse events (focus on checkpoint inhibitors)

Anemia, thrombocytopenia, neutropenia, hemophilia

Nephritis

Myocarditis, pericarditis, vasculitis

Hepatitis

Rash, pruritus, psoriasis, vitiligo, DRESS, Stevens-Johnson syndrome

Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis

Colitis, ileitis, pancreatitis, gastritis

Hyper- or hypothyroidism, hypohysitis, adrenal insufficiency, diabetes

Arthritis, dermatomyositis

Pneumonitis, pleuritis, sarcoid-like granulomatosis

Neuropathy, Guillain-Barré syndrome, myelopathy, meningitis, encephalitis, myasthenia

Multidisciplinary irAE team
irAE database

DRESS, drug reaction with eosinophilia and systemic symptoms; irAEs, immune-related adverse events.

1. Postow et al. N Engl J Med 2018;378:158–68. 2. Champiat et al. Ann Oncol 2016;27:559–74. 3. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

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Allogeneic stem cell transplantation

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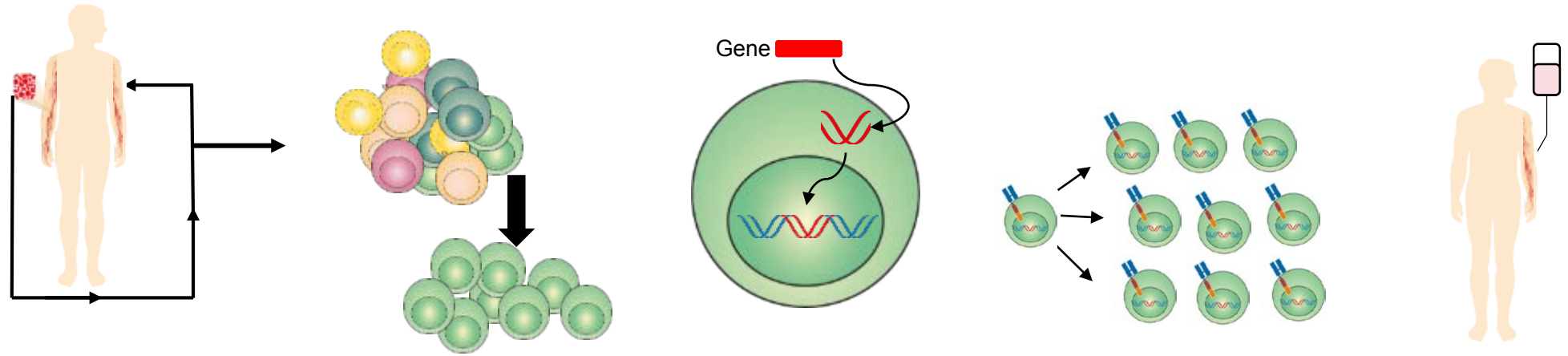
T cell therapy

CAR T cells: the process

An overview of the CAR T-cell immunotherapy clinical process[1]



Apheresis of mononuclear cells

T cells are selected and activated in vitro

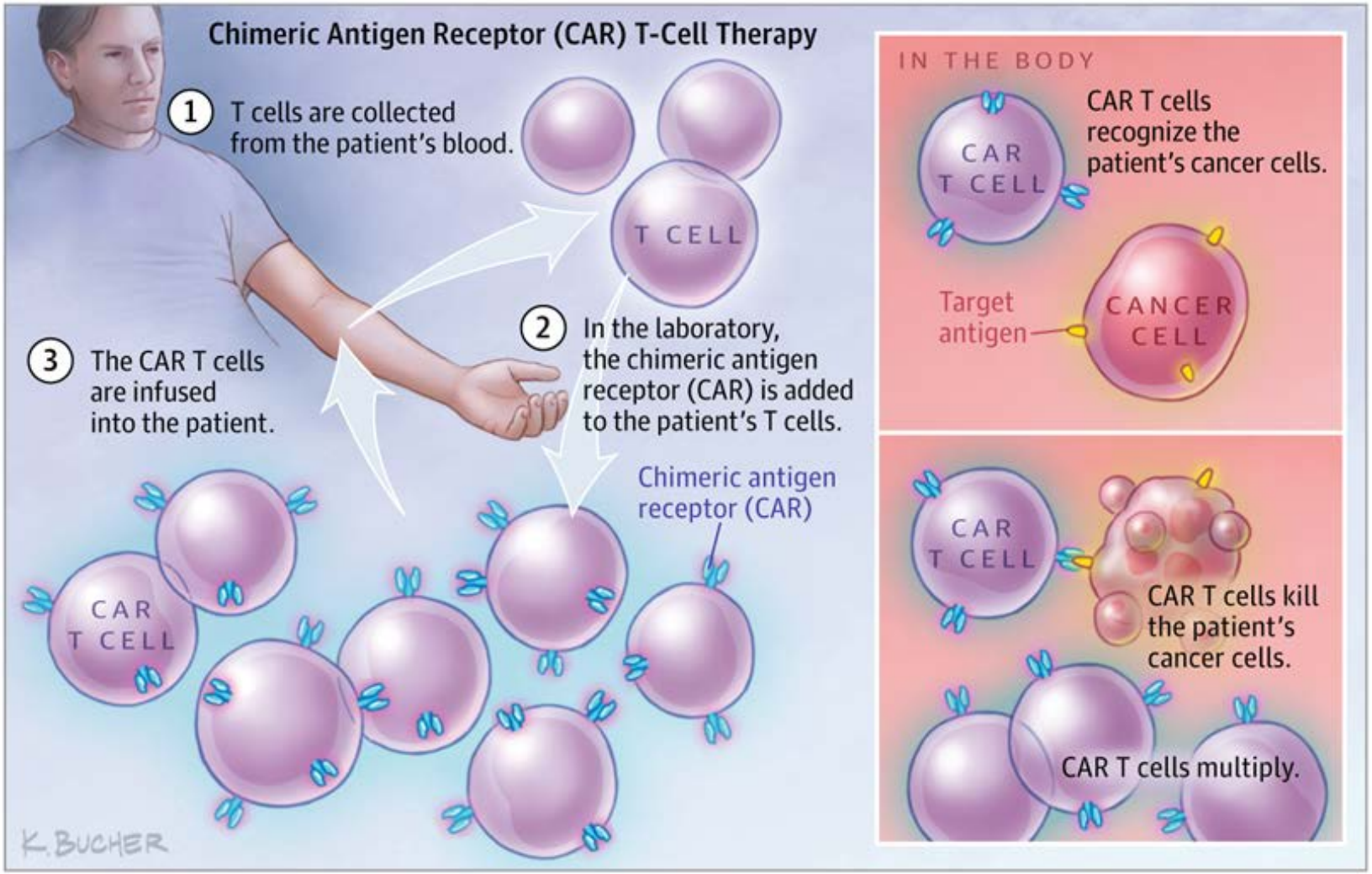
CAR construct is transferred into the T cells

Transduced CAR T cells are expanded

CAR T cells are reinfused into the patient

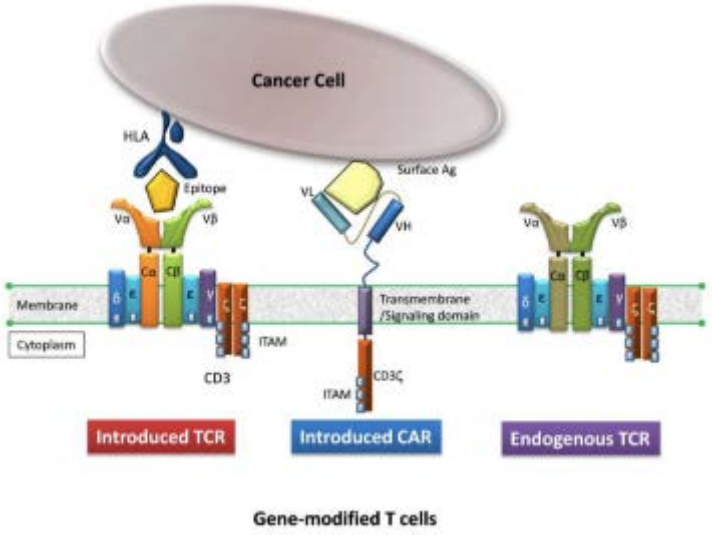
1. Davila et al. OncoImmunology 2012;1:1577–83.

CAR T cell therapy: what happens *in vivo*?

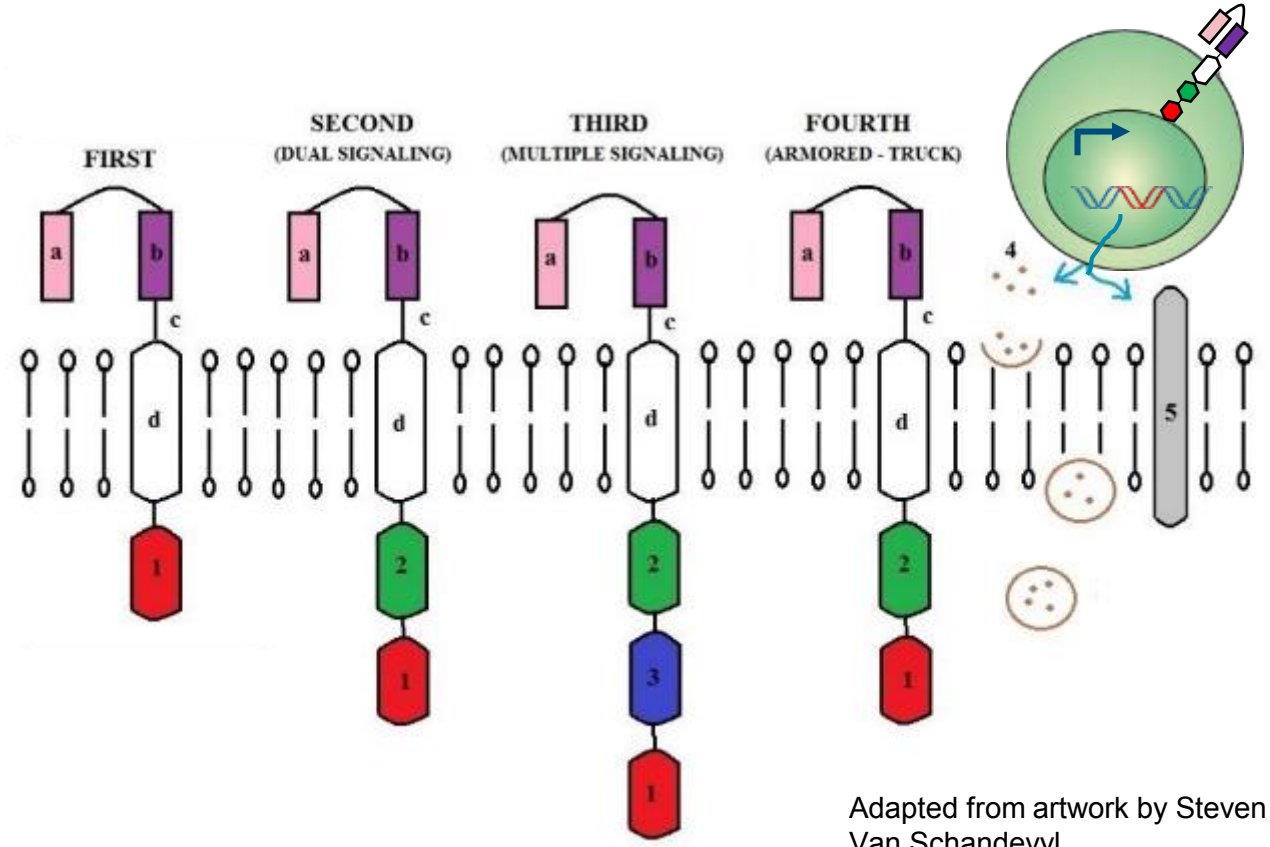


Keuhn B JAMA. 2017;318:22:2167-69.

Four generations of CAR T-cell design



Adapted from Fujiwara H. 2014.



Adapted from artwork by Steven Van Schandevyl.

CAR, chimeric antigen receptor; IL-12, interleukin 12; scFv, single-chain variable fragment; TRUCK, T cell redirected for universal cytokine mediated killing.
1. Fujiwara H, Pharmaceuticals, 2014. 2. Kerre T. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original artwork kindly provided by Steven Van Schandevyl.

CAR T cell therapy: antigen targets in clinical trials

CAR T cells have been engineered to target many different antigens to treat various cancers

Hematologic malignancies[1]

Antigen	Cancer
BCMA	MM
CD123	AML, leukemia, lymphoma
CD138	MM
CD16V	DLBCL, MCL, PMBCL, FL
CD19	CLL, NHL, ALL, DLBCL, PMBCL, MCL, DLBCL transf. FL, lymphoma, FL, PLL, DMBCL, leukemia, SLL, BAL, HL, MLBCL, MM DLBCL
CD19/CD20	Leukemia, lymphoma
CD19/CD22	ALL, CLL, PLL, DLBCL, FL, MCL, leukemia, Lymphoma, SLL, MZL, NHL
CD20	FL, ALL, NHL, DLBCL, MCL, leukemia, lymphoma
CD22	NHL, HL, lymphoma, CD30+ cancer
CD30	AML
CD33	B cell malignancies
CD38[2]	CD70+ cancer
CD70	B cell malignancies
CD123[2]	CLL, NHL, MM
Ig k	CLL
IL-1RAP	MM, AML, MDS
Lewis Y	AML, MDS, MM
NKG2D ligand	CLL, SLL, MCL, ALL
ROR1	

Solid malignancies[1]

Antigen	Cancer
CAIX	Renal cell carcinoma
CEA	Liver metastases, liver, adenocarcinoma, gastric, colorectal, breast
C-MET	Breast
EGFR	EGFR+ solid tumors, GBM, glioma
EGFRvIII	Glioma, GBM, glioblastoma
EpCam	Liver, stomach, breast
EphA2	Malignant glioma
ErbB2/Her2	HER2+ malignancy, sarcoma, GBM, head and neck, breast, glioblastoma, Metastatic mesothelioma
FAP	Ovarian
FR-a	Neuroblastoma, sarcomas
GD2	Hepatocellular carcinoma, LSCC, GPC3+ solid tumor
GPC3	Malignant glioma, brain and CNS
IL-13Ra2	Neuroblastoma
L1-CAM	MPM, MPDAC, malignant pleural disease, pancreatic, breast, mesothelin+ tumors
Mesothelin	Hepatocellular carcinoma, NSCLC, TNBC, PC, malignant glioma, CC, GC
MUC1	Ovarian
MUC16ecto	GBM
PD-L1	Pancreatic
PSCA	Prostate
PSMA	NSCLC, breast cancer (TNBC)
ROR1	various
VEGFR-2	

1. Hartmann et al. EMBO Mol Med 2017;9:1183–97. 2. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03125577. Accessed April 2018.

CAR T cell therapy in hematology

Hematology

- B cell malignancies (CD19, 20, 22)
- Multiple myeloma (CD138, CD38, CD56, LeY)
- AML (CD33, CD123, LeY, NKG2D ligands)
- Hodgkin lymphoma, T cell lymphoma (CD30)
- ……

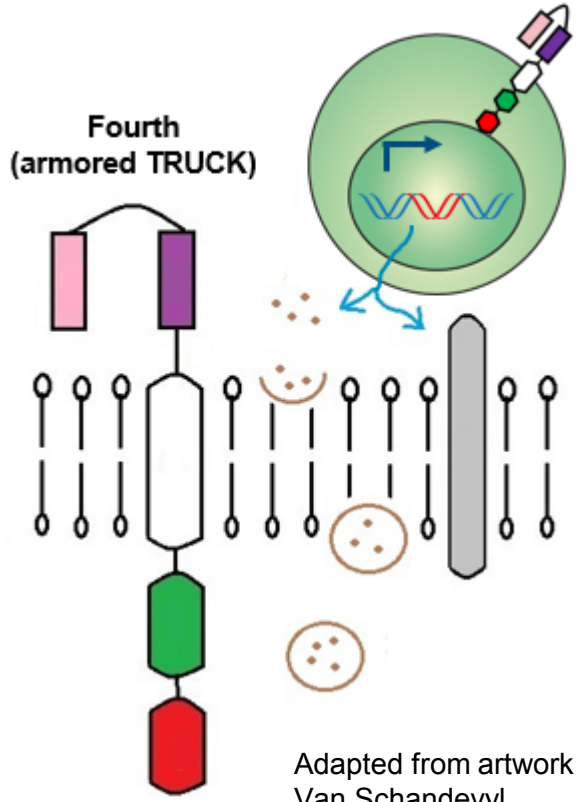
Oncology (solid tumours)

- Challenge! → TRUCKs
- …..

Efficacy of CAR T-cell therapies: additional challenges for solid tumors

- The anatomical location
- The heterogeneity of the tumor cells
- The immune-suppressing microenvironment

Fourth-generation CARs = TRUCKs



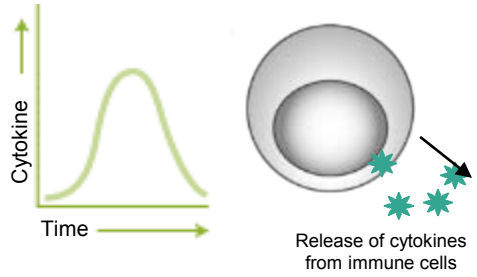
Adapted from artwork by Steven Van Schandevyl.

CAR, chimeric antigen receptor; TRUCK, T cell redirected for universal cytokine mediated killing.

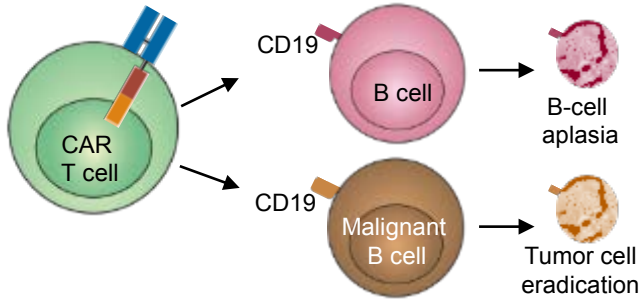
1. Kerre. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original awork kindly provided by Steven Van Schandevyl.

CAR T cell therapy: selected adverse events

Reported/potential toxicities following the use of CAR T cells[1]



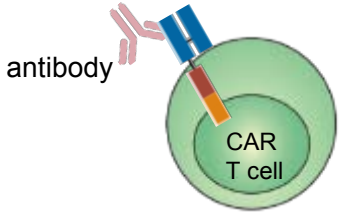
To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6–90% in clinical trials)[2]



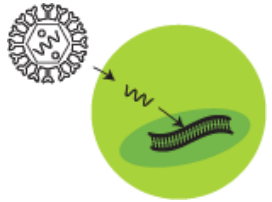
The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus, and seizure, has been reported in patients who received CD19-specific CAR T cells[1] (12–48% in clinical trials)[2]

Several dermatologic complications have also been described, including secondary cutaneous malignancies[3]



Both cellular and humoral rejection of CAR T cells have been demonstrated due to the immunogenicity of foreign protein. Host reaction can manifest as anaphylaxis or allergy[1]

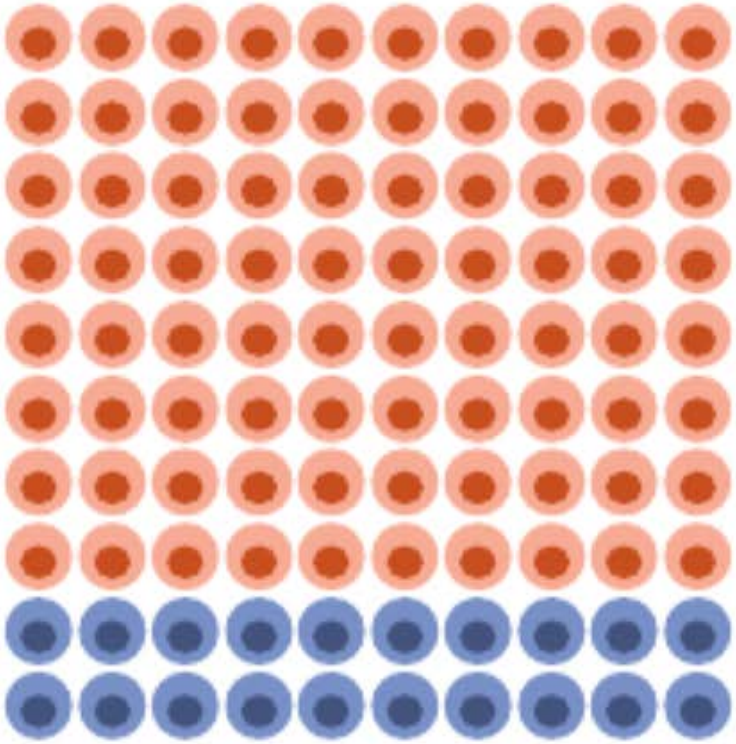


The risk of insertional oncogenesis following gene transfer into T cells is seemingly low; however, investigators must remain vigilant and adhere to strict monitoring[1]

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine-release syndrome.

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Rubin et al. J Am Acad Dermatol 2016;75:1054–7

CAR T cell therapy: clinical trials and targets



>240 CAR T cell trials registered at clinicaltrials.gov

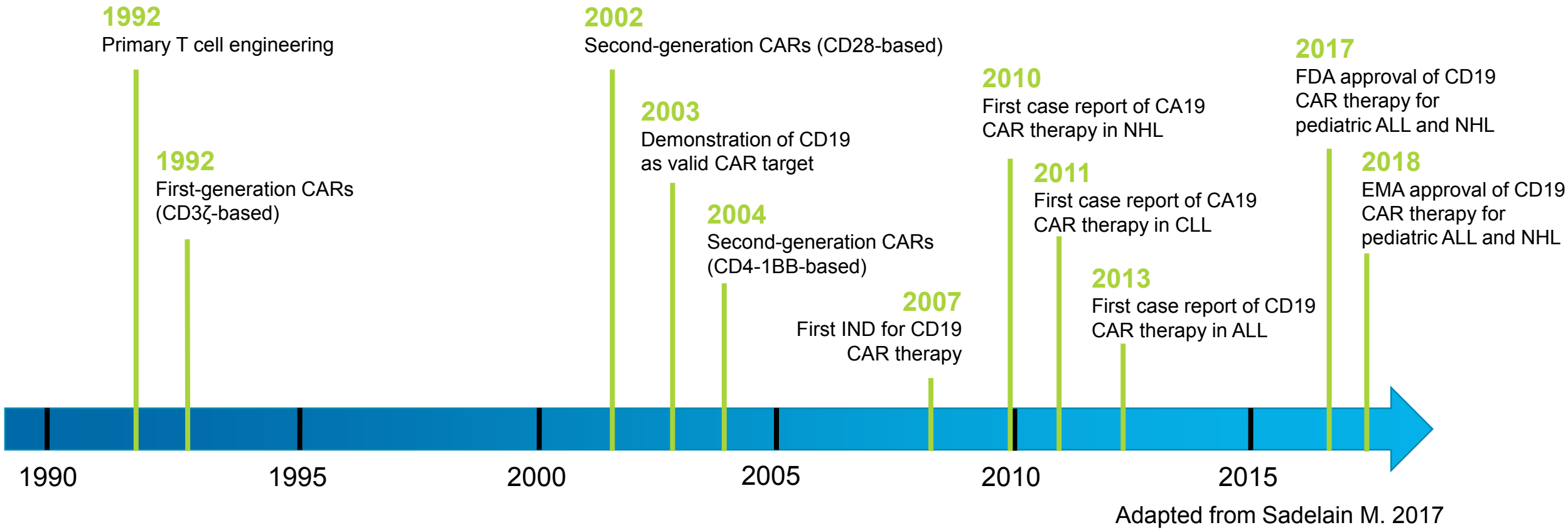
>80 CAR targets investigated in preclinical studies

>40 Biotech companies with an active CAR program

>20 CAR targets investigated in clinical trials

Sadelain M. Cell 2017;171:7:1471.

CAR T cell therapy: timeline



Adapted from Sadelain M. 2017

Sadelain M, Cell 2017;171:7:1471.

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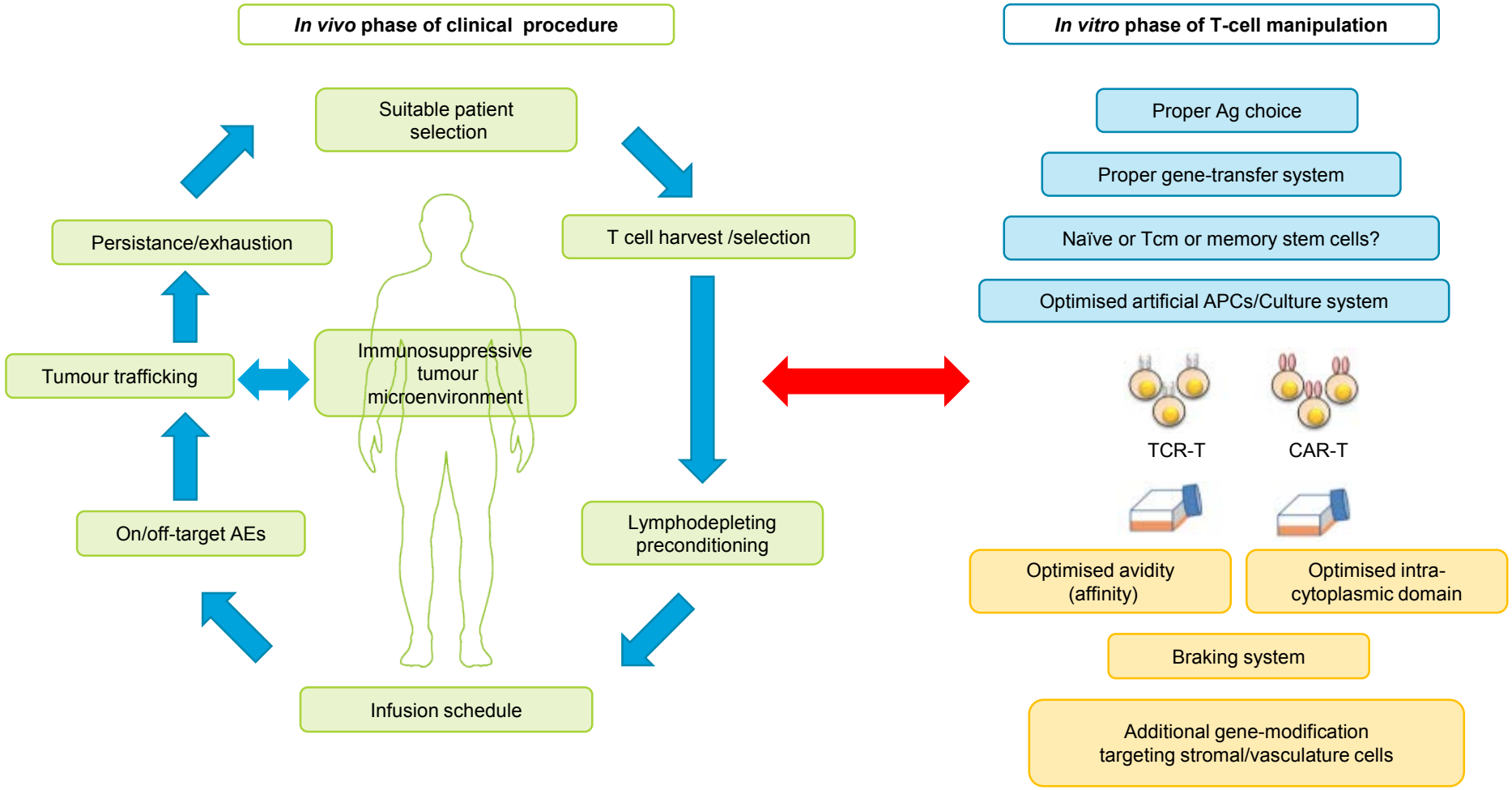
CAR T cell therapy: CAR at UZ Gent

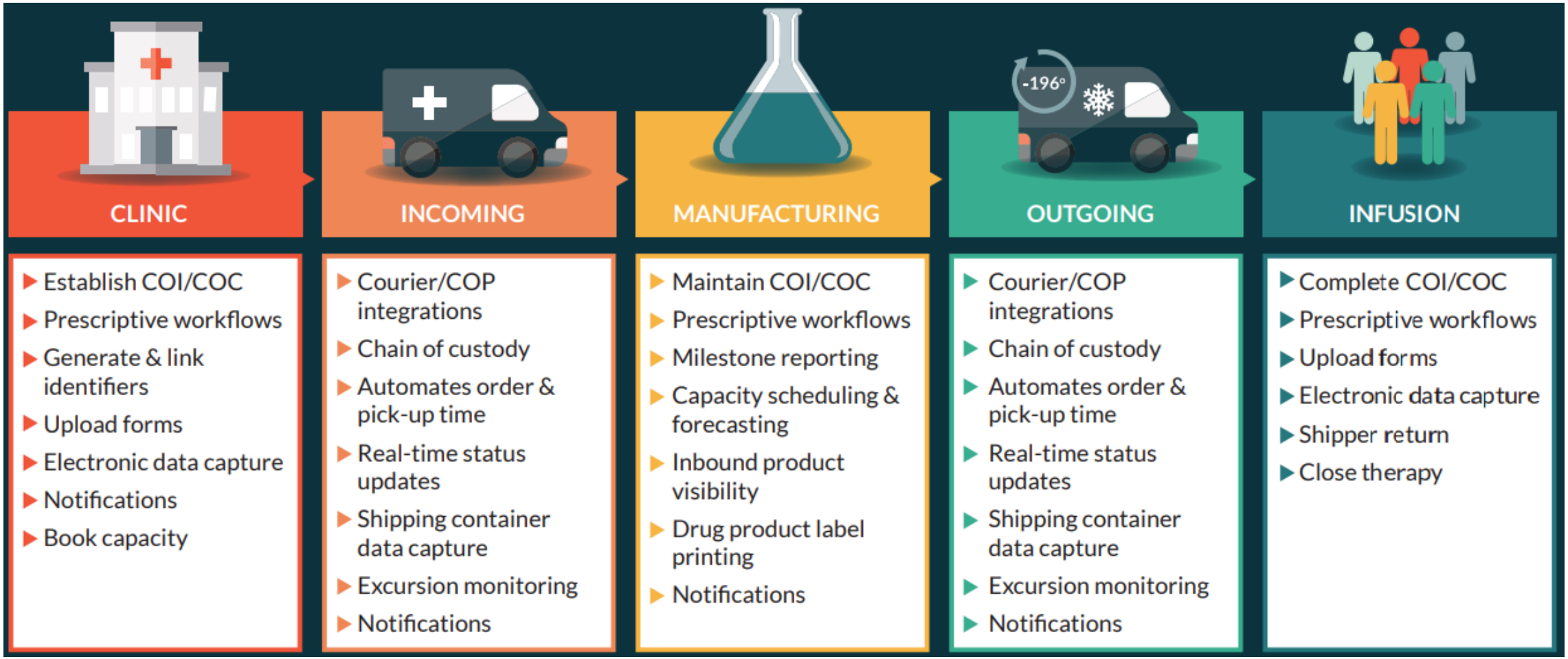
- First CAR T cell therapy began 3 years ago
- 12 trials:
  - 1 closed
  - 5 actively recruiting
  - 6 start-up
- 16 patients

CAR T cell therapy: challenges



AE, adverse event; Ag, antigen; APC, antigen presenting cells; CAR-T, chimeric antigen receptor therapy; Tcm, central memory T; TCR-T, T cell receptor therapy.

CAR T cell therapy: procedure



COP, Cell Orchestration Platforms, COP.
Lamb M et al. Cell Gene Therapy Insights 2017;3:10:815-33.

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Click on the vials to discover the different forms of immunotherapy.

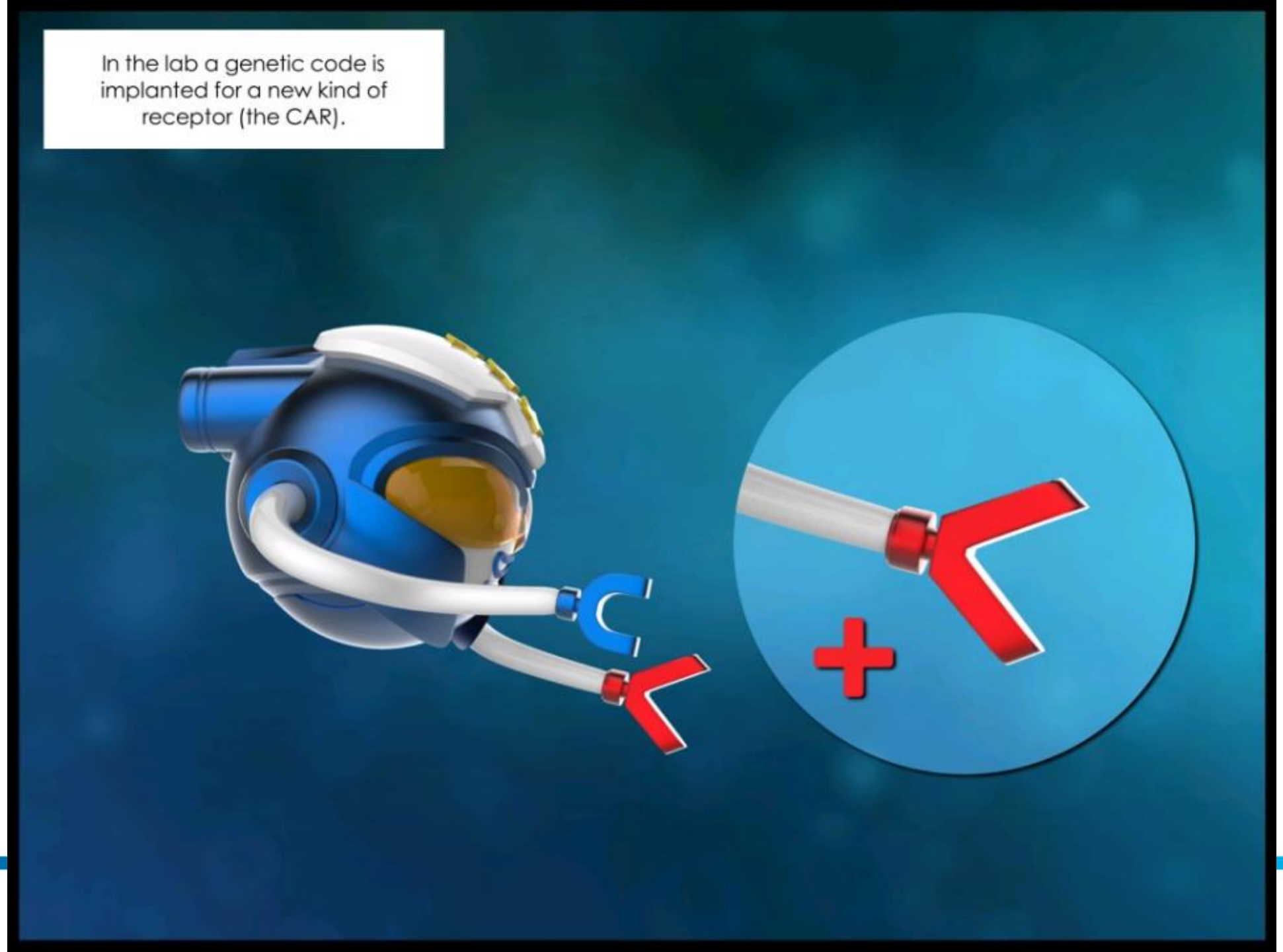
checkpoint inhibitors

CAR T-cell therapy

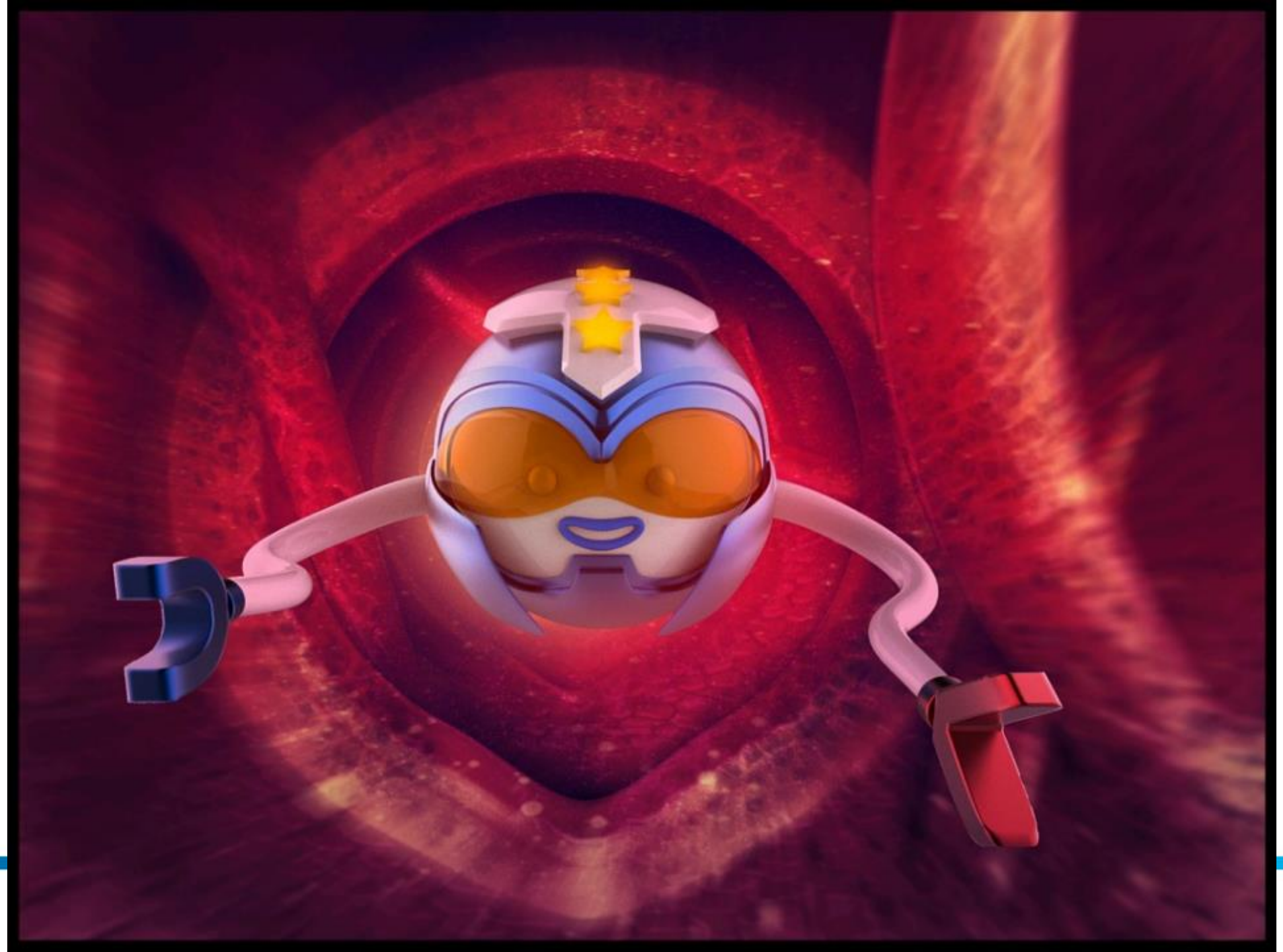
BiTes

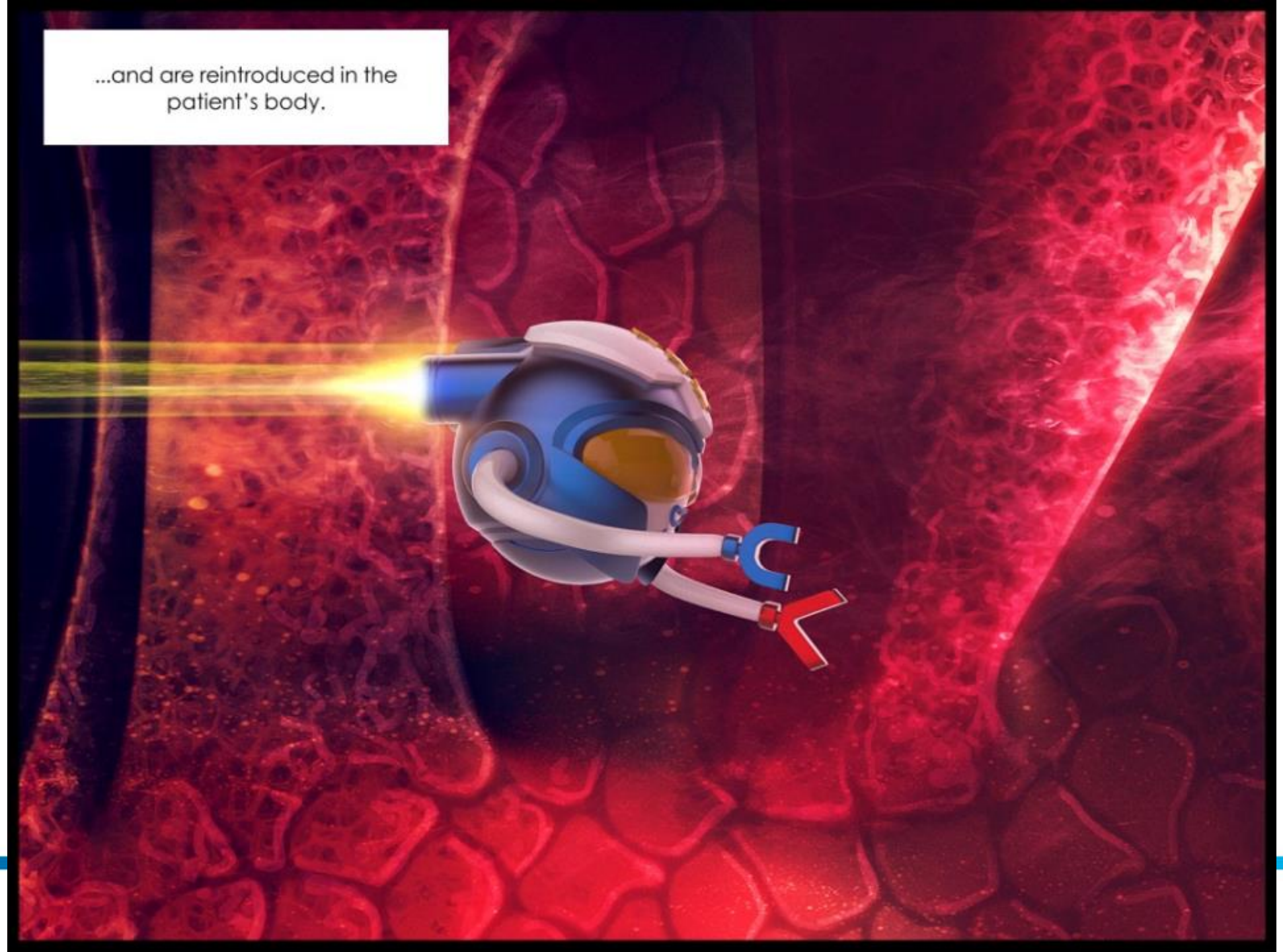
Back to start

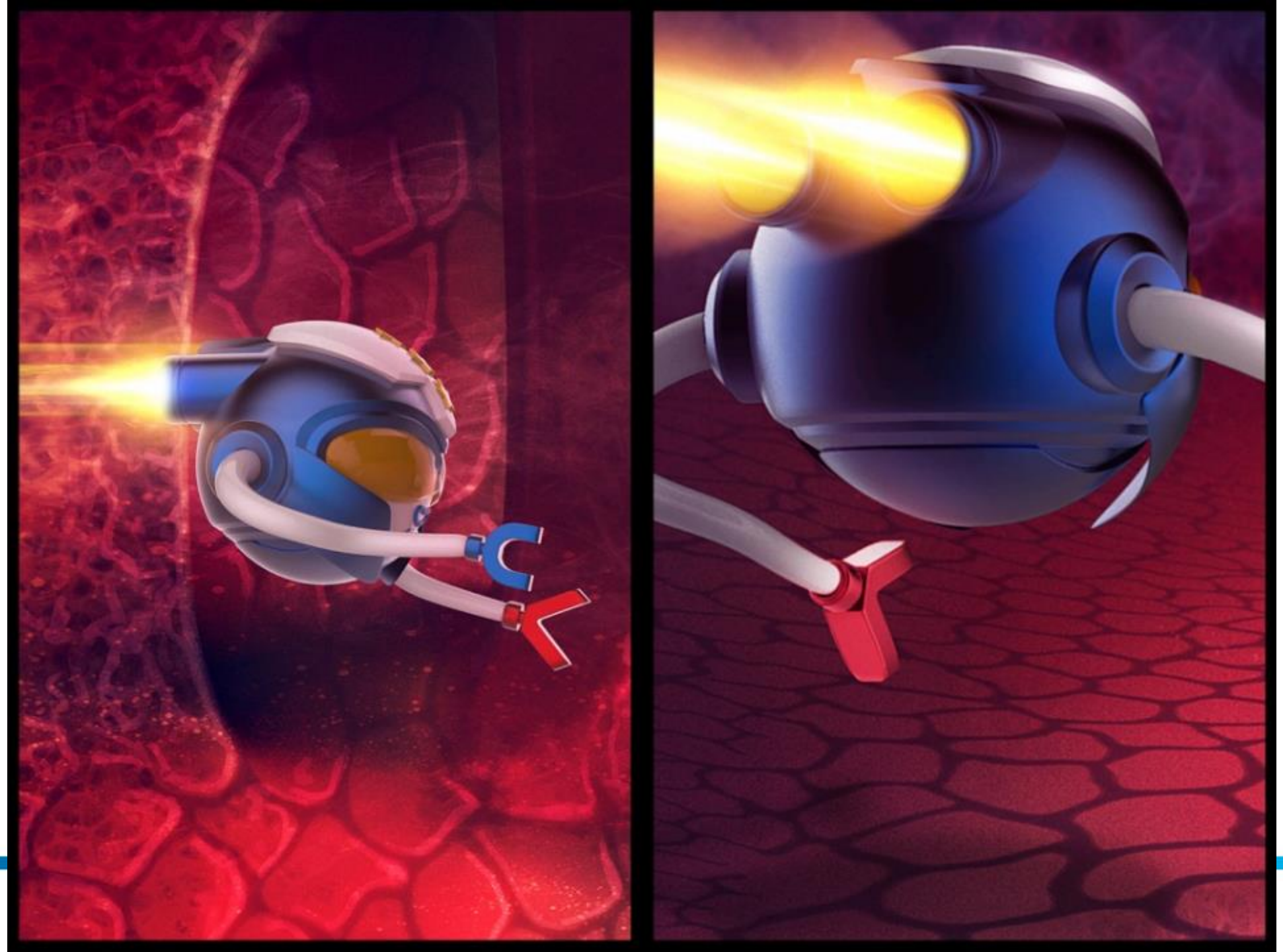

Fortunately science has found a solution: CAR T-cell therapy.

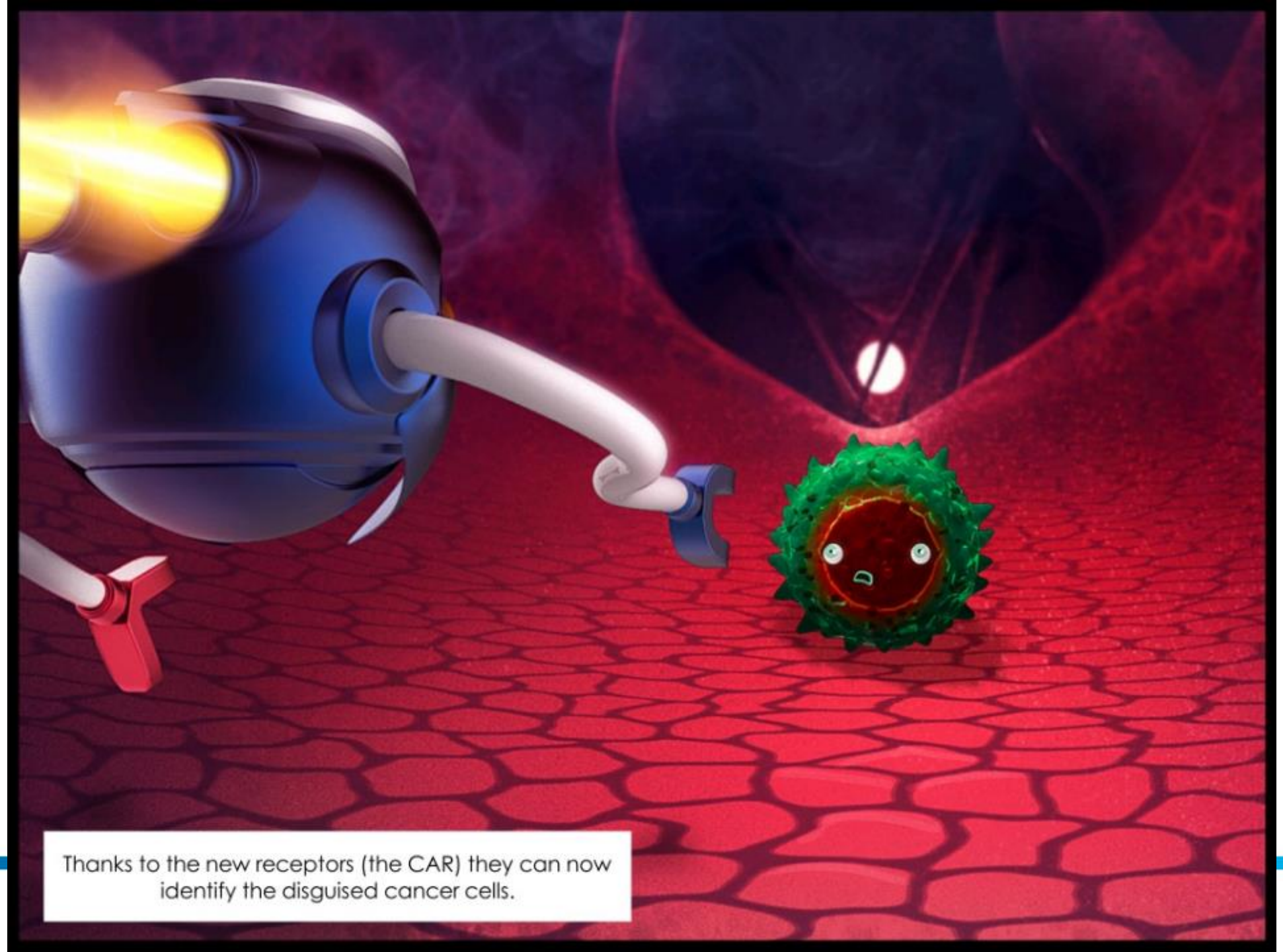

In the lab a genetic code is implanted for a new kind of receptor (the CAR).

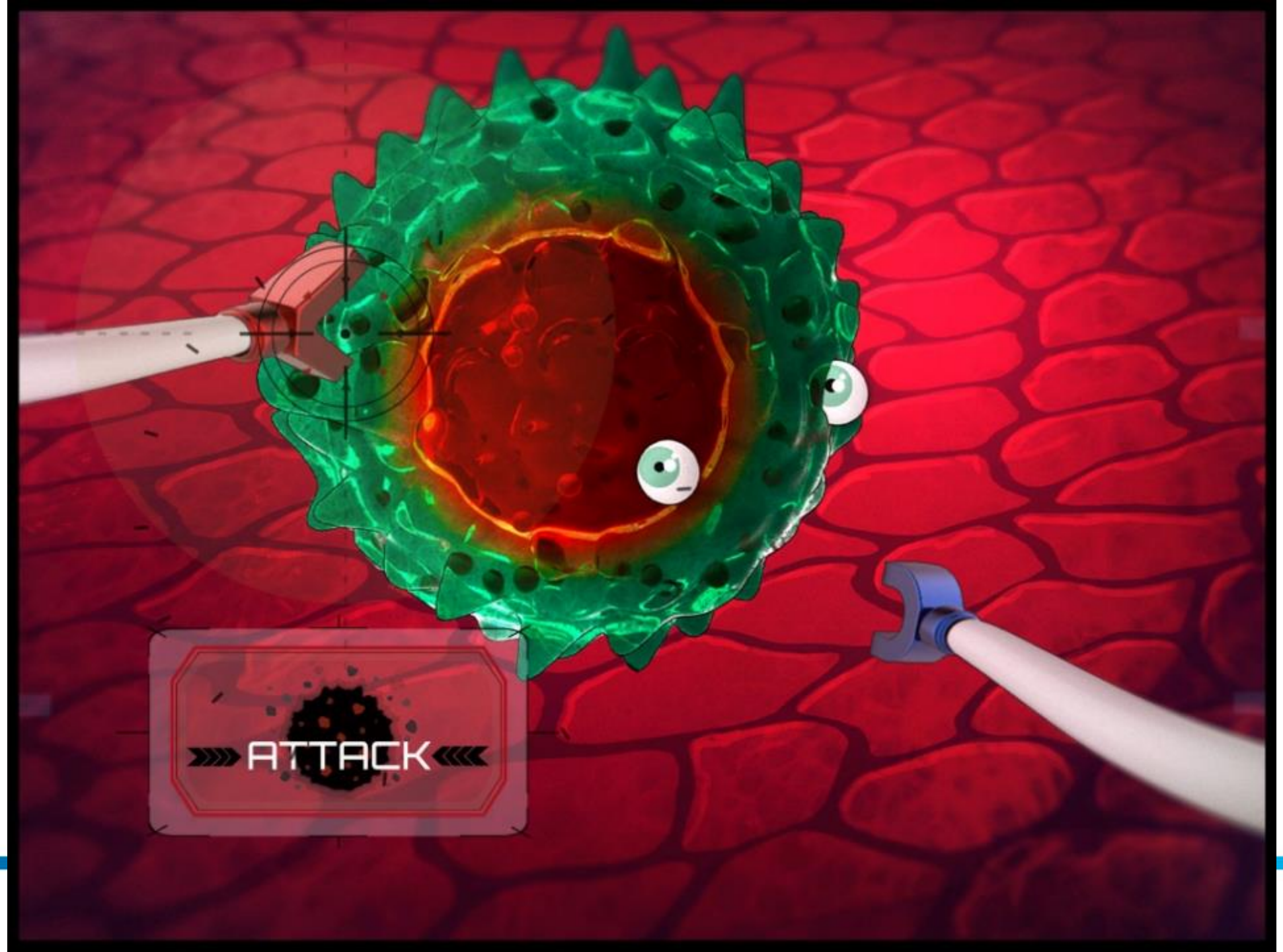

The modified T-cells are now
CAR T-cells...



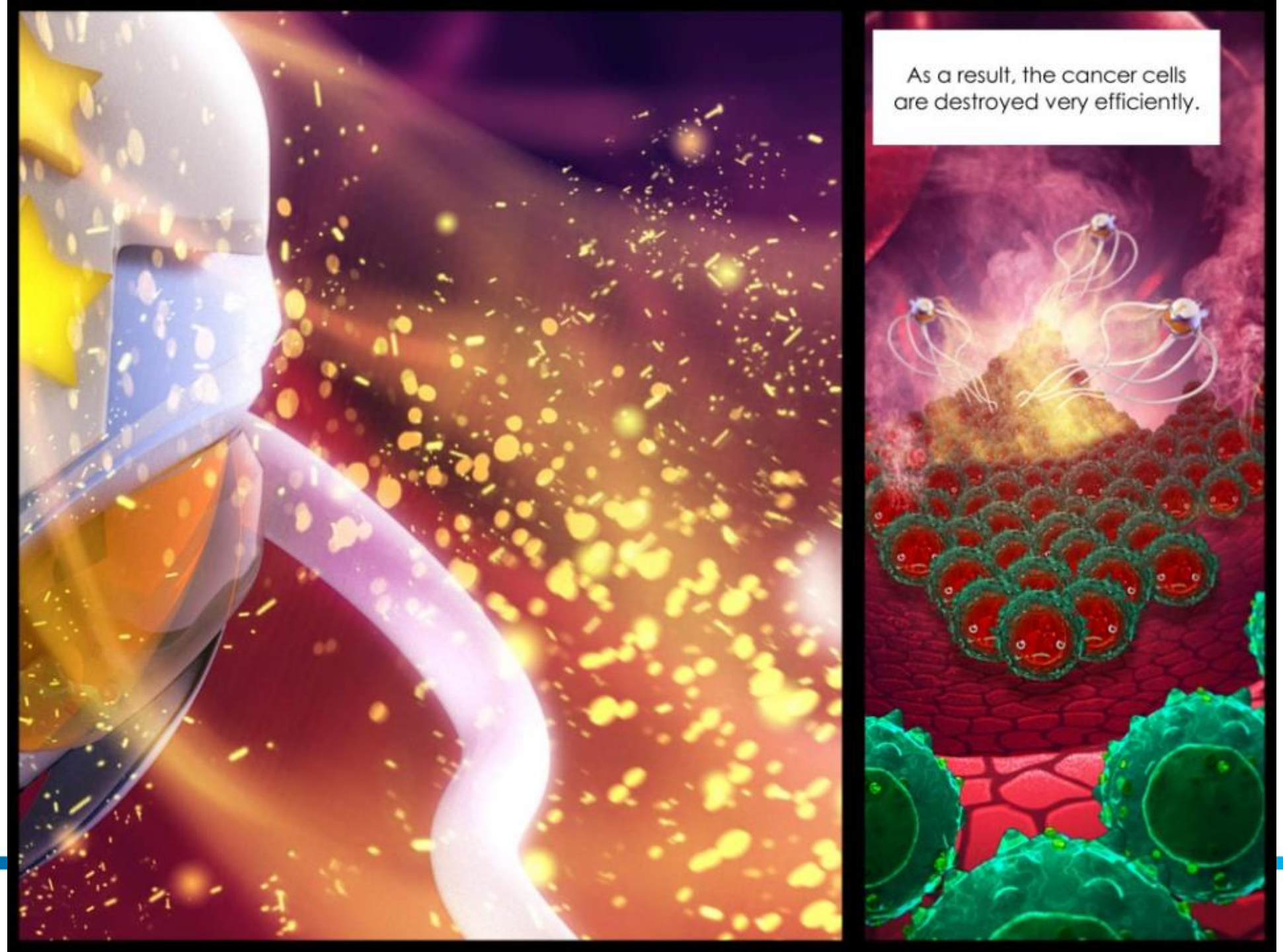

...and are reintroduced in the patient's body.

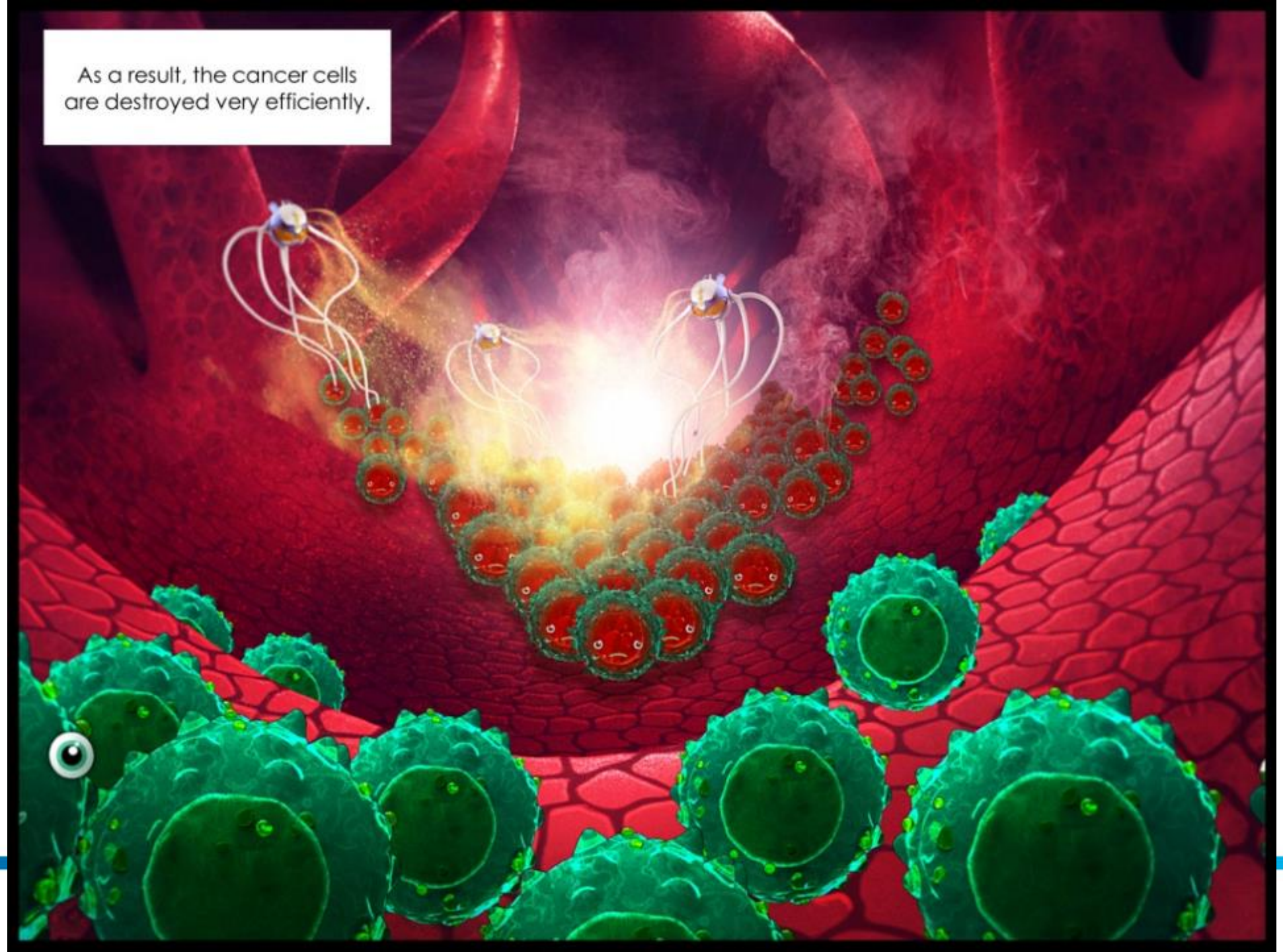



Thanks to the new receptors (the CAR) they can now identify the disguised cancer cells.


ATTACK


The CAR has also made the T-cell stronger.


As a result, the cancer cells are destroyed very efficiently.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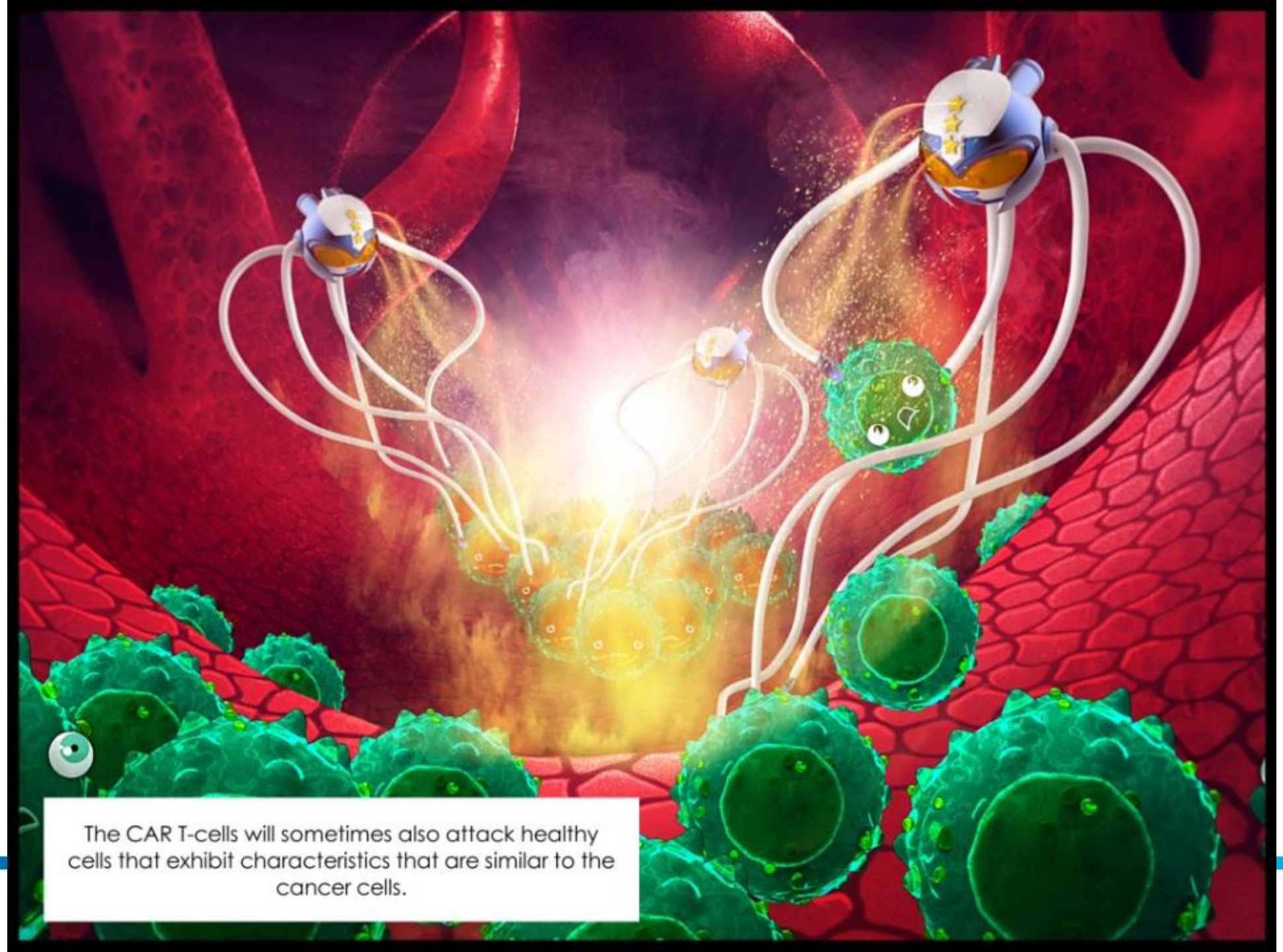
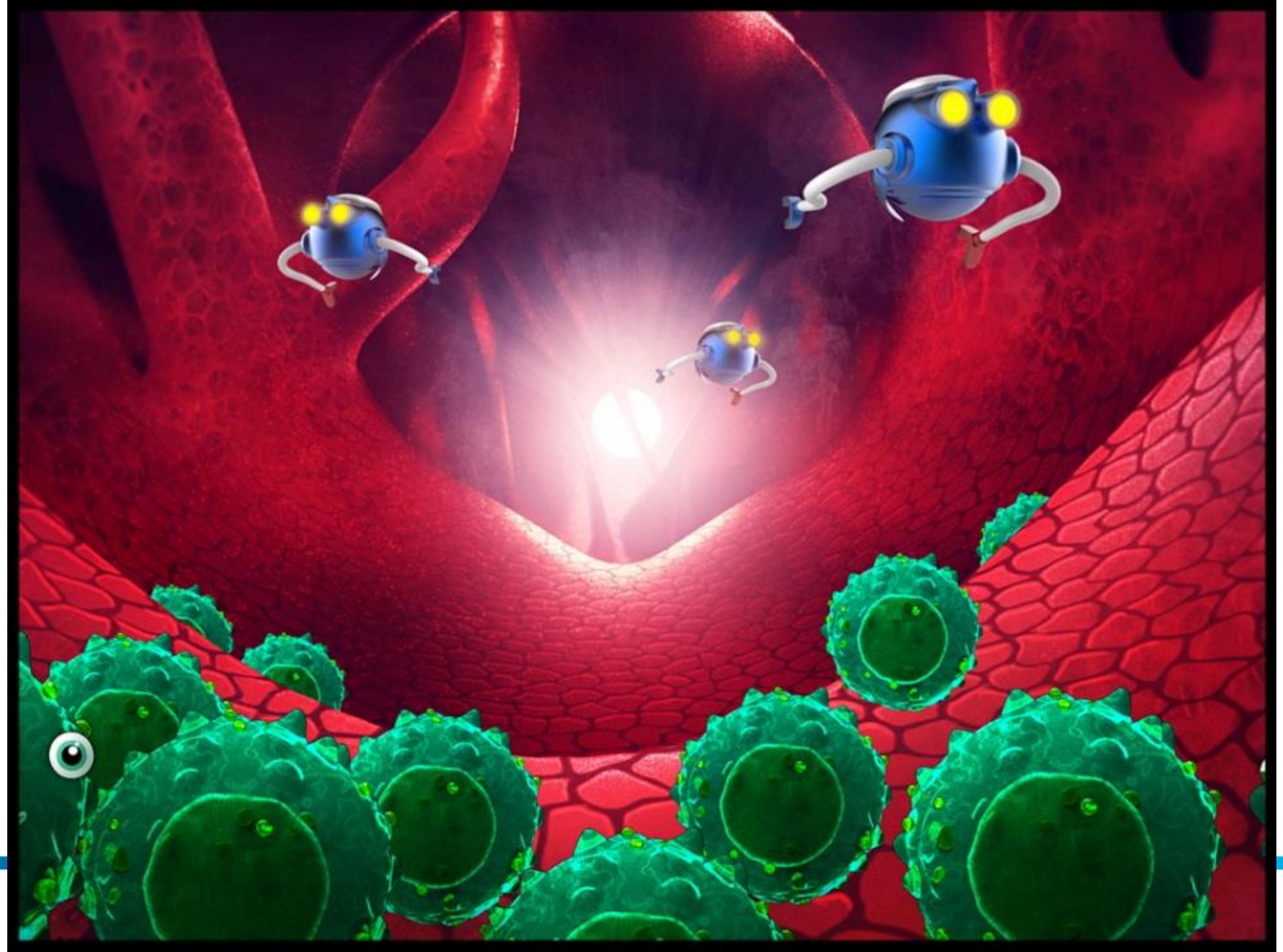
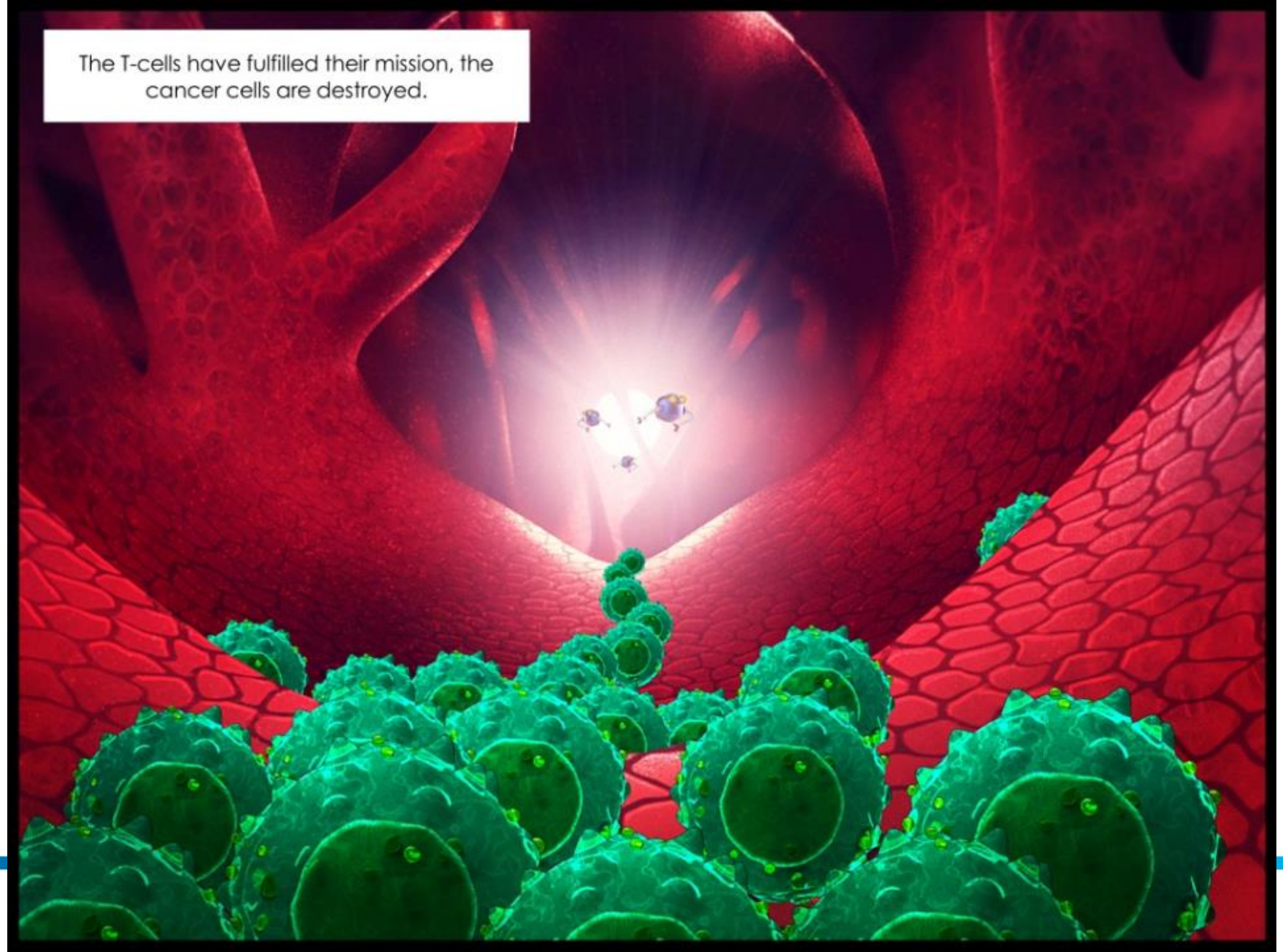

The CAR T-cells will sometimes also attack healthy cells that exhibit characteristics that are similar to the cancer cells.




The T-cells have fulfilled their mission, the cancer cells are destroyed.

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Associate Professor Ugent
Senior clinical resaercher FWO
Program director of the Stem Cell Program UZG

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