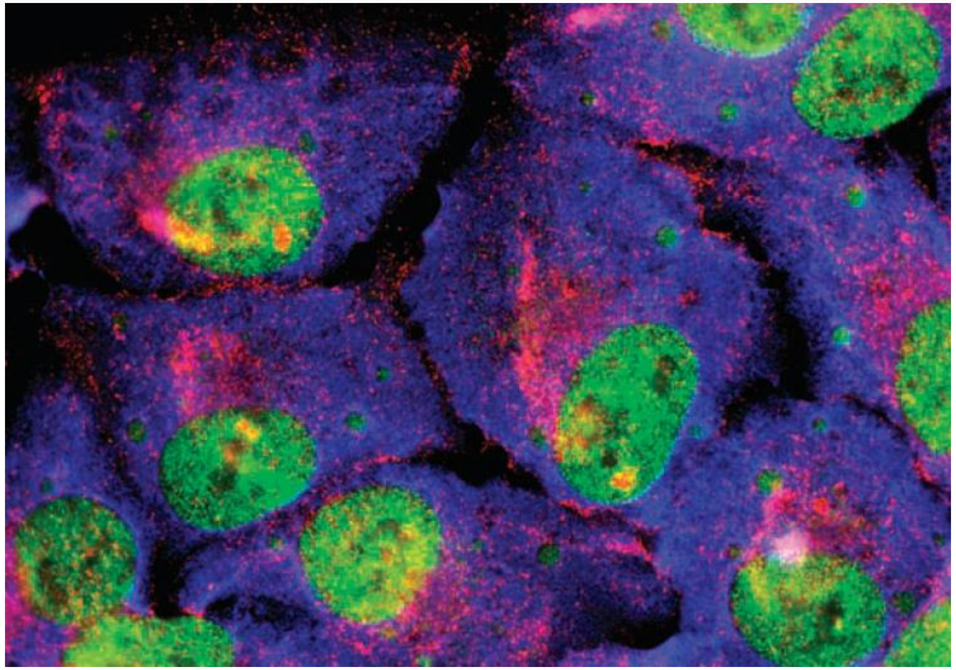
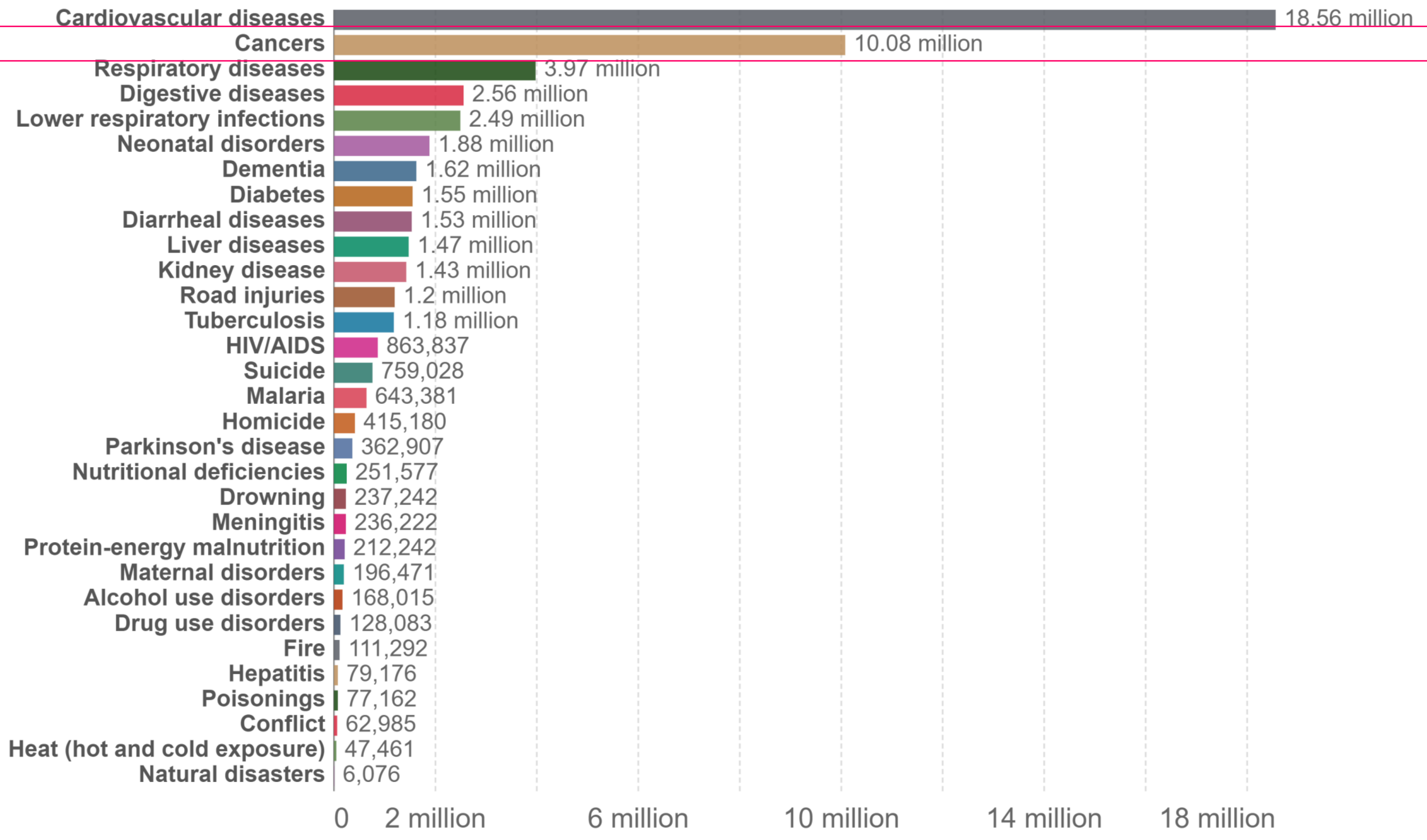
“Imunidade contra tumores” e Imunoterapia



Juliana Moreira Mendonça Gomes

Number of deaths by cause, World, 2019

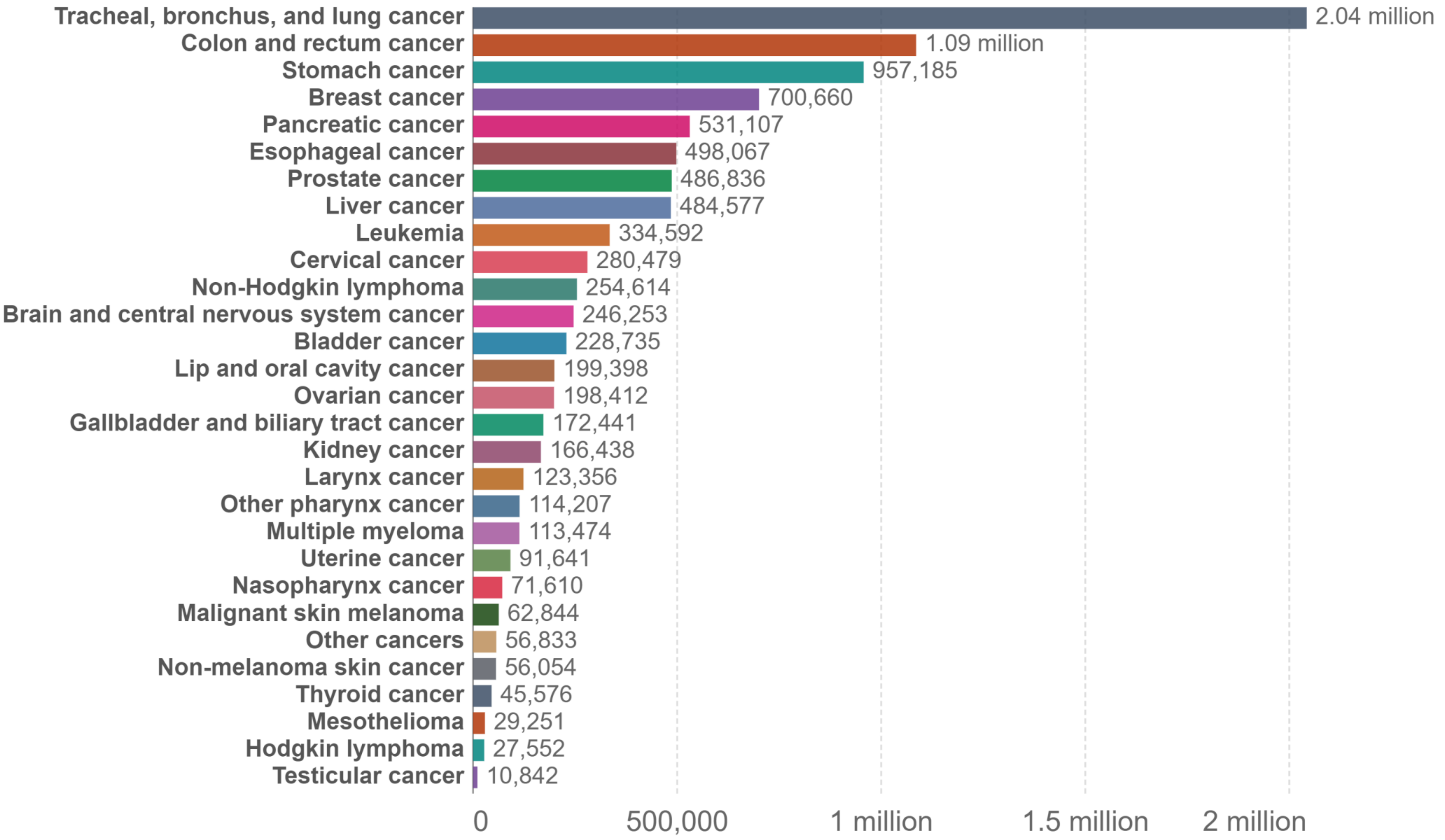
Our World in Data



Source: IHME, Global Burden of Disease

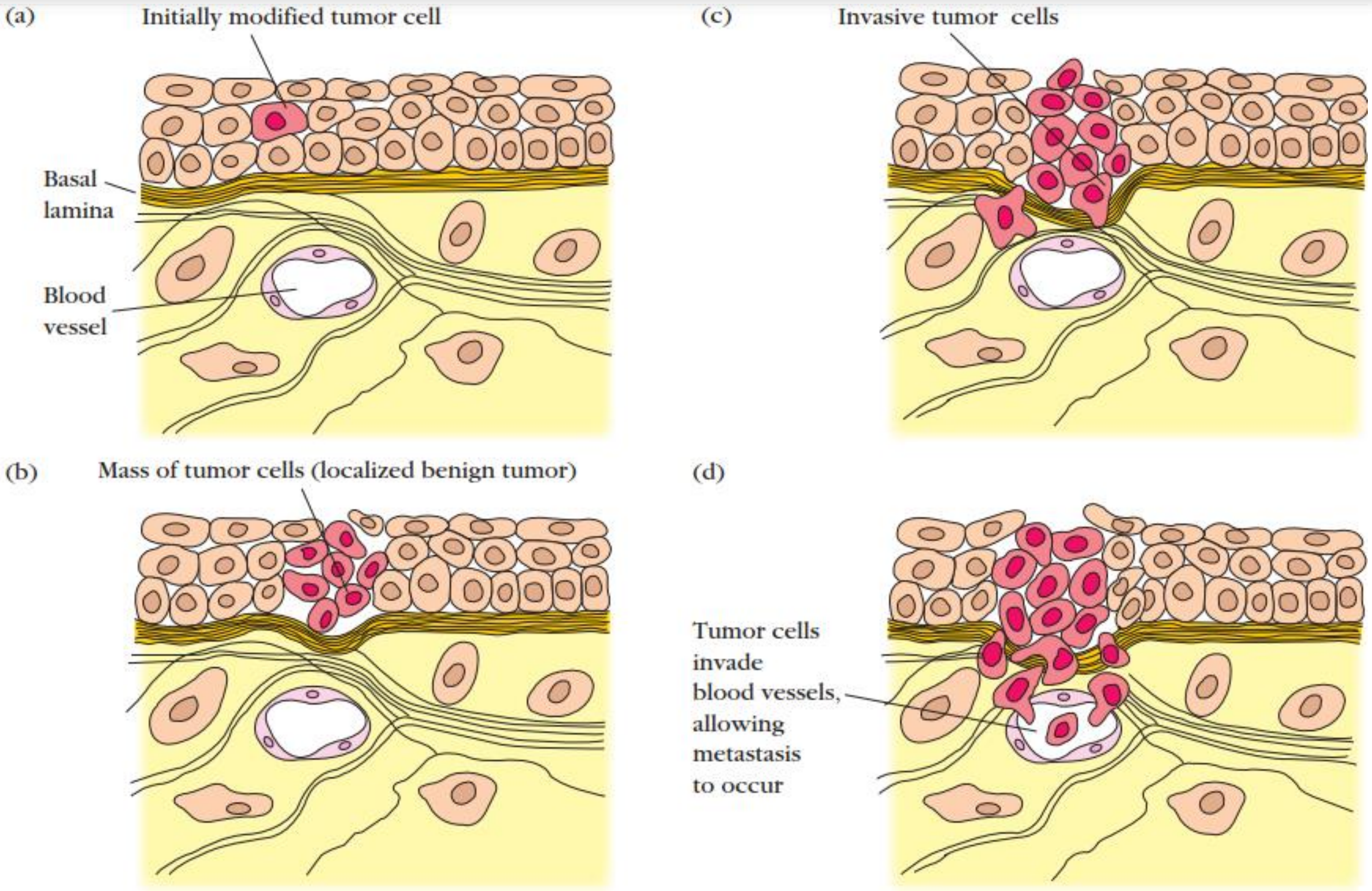
Cancer deaths by type, World, 2019

Total annual number of deaths from cancers across all ages and both sexes, broken down by cancer type.



Source: IHME, Global Burden of Disease (GBD)

Como ocorre o câncer?



Kuby 7ª edição

Hallmarks do câncer – ano 2000

“Sustentam proliferação”

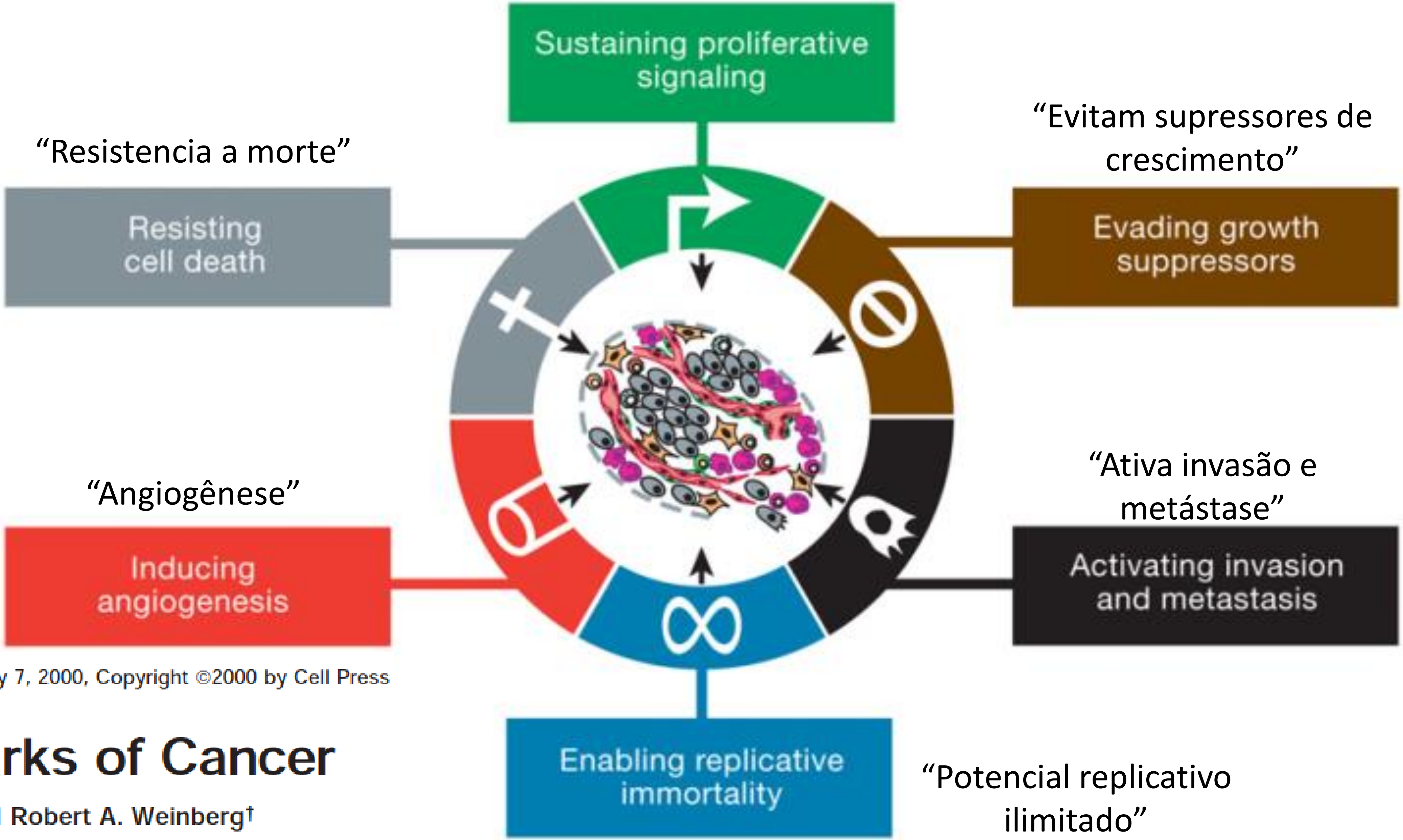
“Resistencia a morte”

“Evitam supressores de crescimento”

“Angiogênese”

“Ativa invasão e metástase”

“Potencial replicativo ilimitado”



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

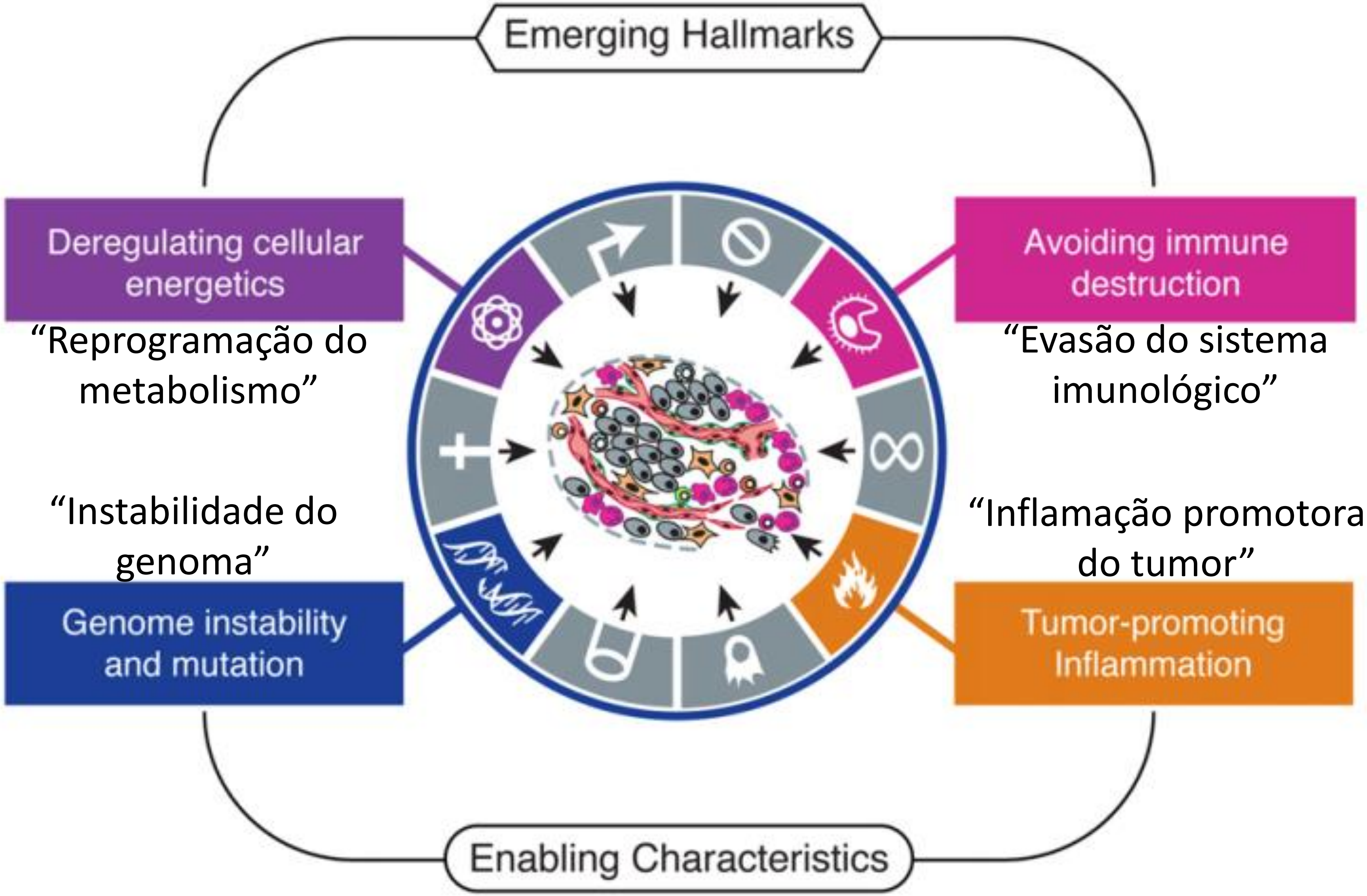
Douglas Hanahan* and Robert A. Weinberg†

Hallmarks do câncer – ano 2011

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Cell *144*, March 4, 2011 ©2011 Elsevier Inc.



“Reprogramação do metabolismo”

“Evasão do sistema imunológico”

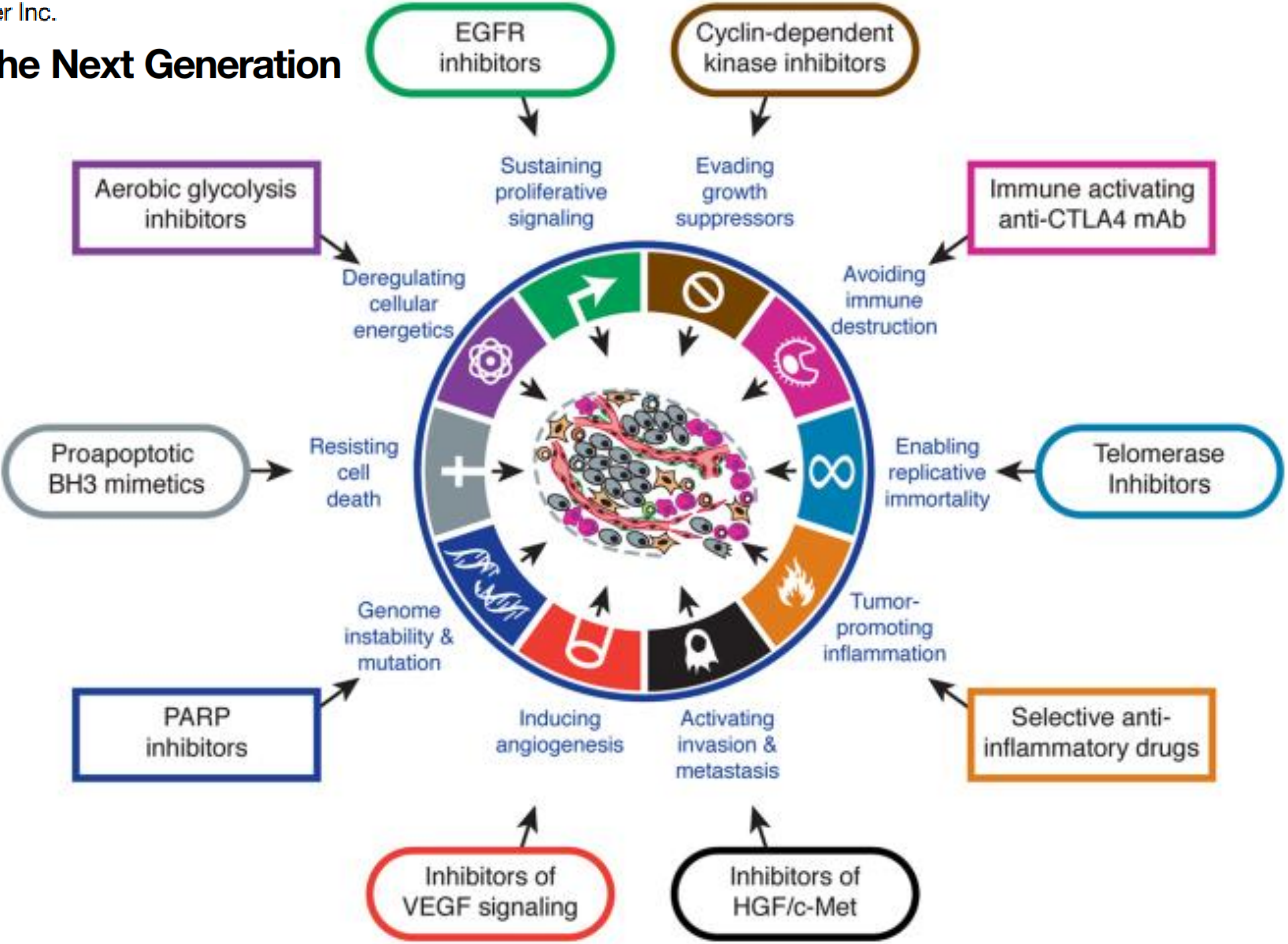
“Instabilidade do genoma”

“Inflamação promotora do tumor”

Cell *144*, March 4, 2011 ©2011 Elsevier Inc.

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]



Hallmarks do câncer – ano 2022

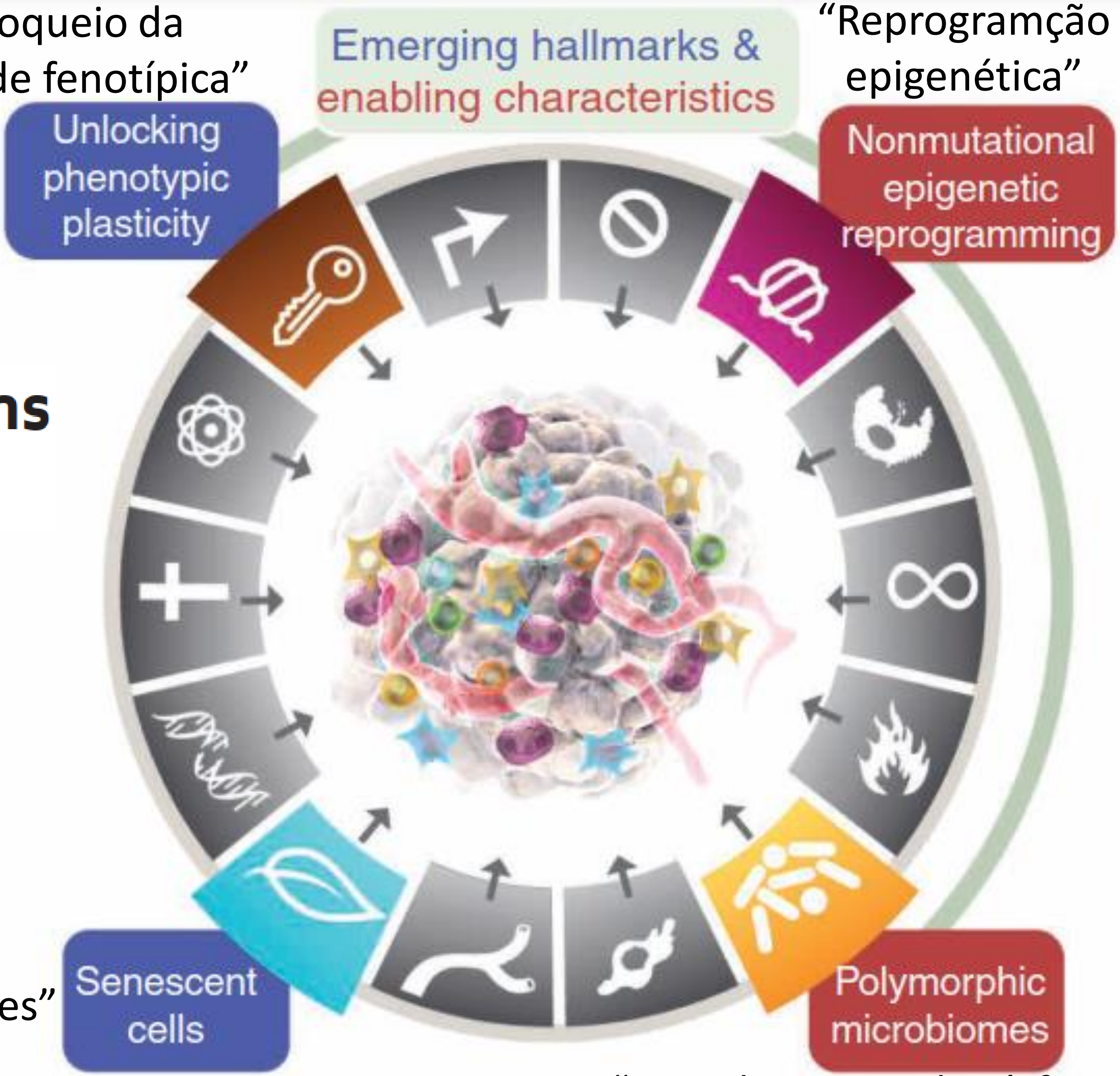
“Desbloqueio da plasticidade fenotípica”

“Reprogramção epigenética”

JANUARY 2022 CANCER DISCOVERY | 31

Hallmarks of Cancer: New Dimensions

Douglas Hanahan

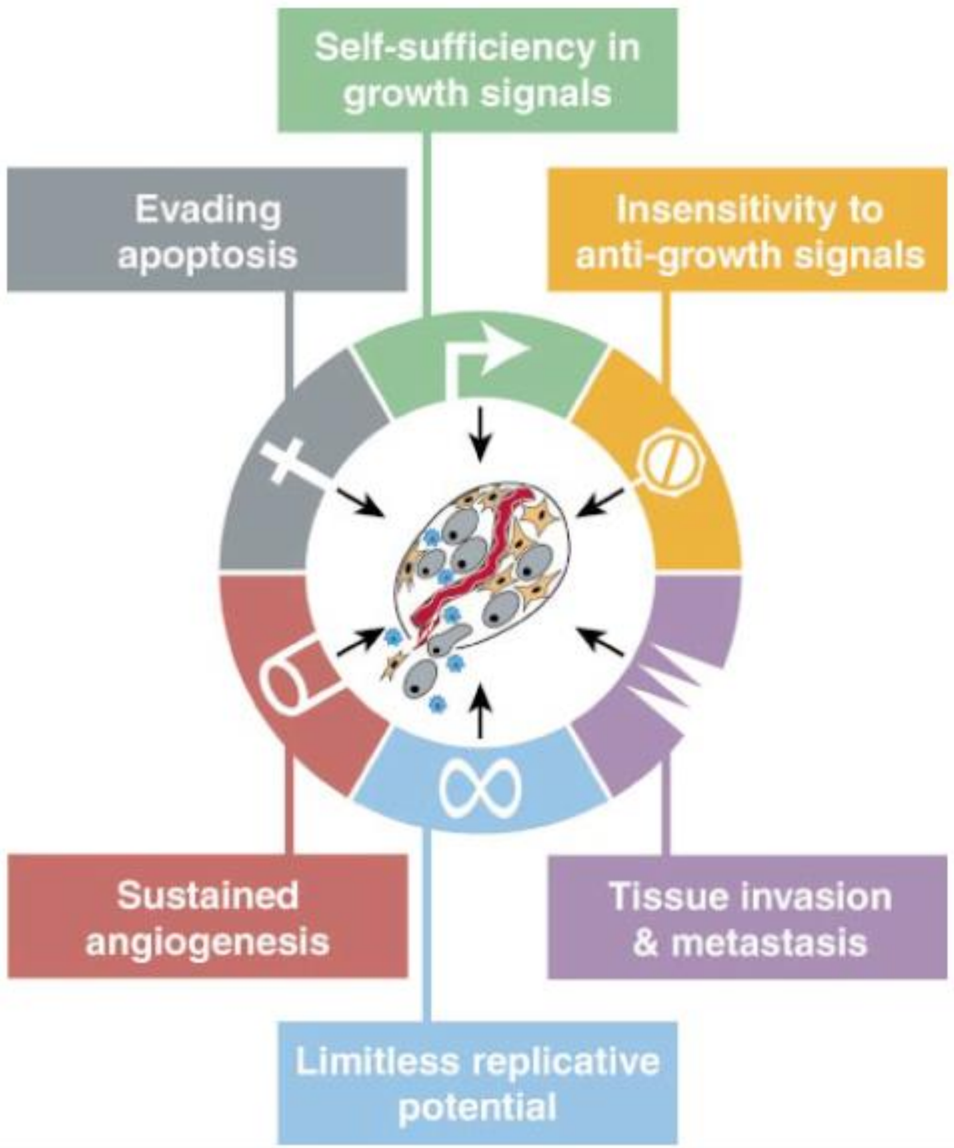


“Células senescentes”

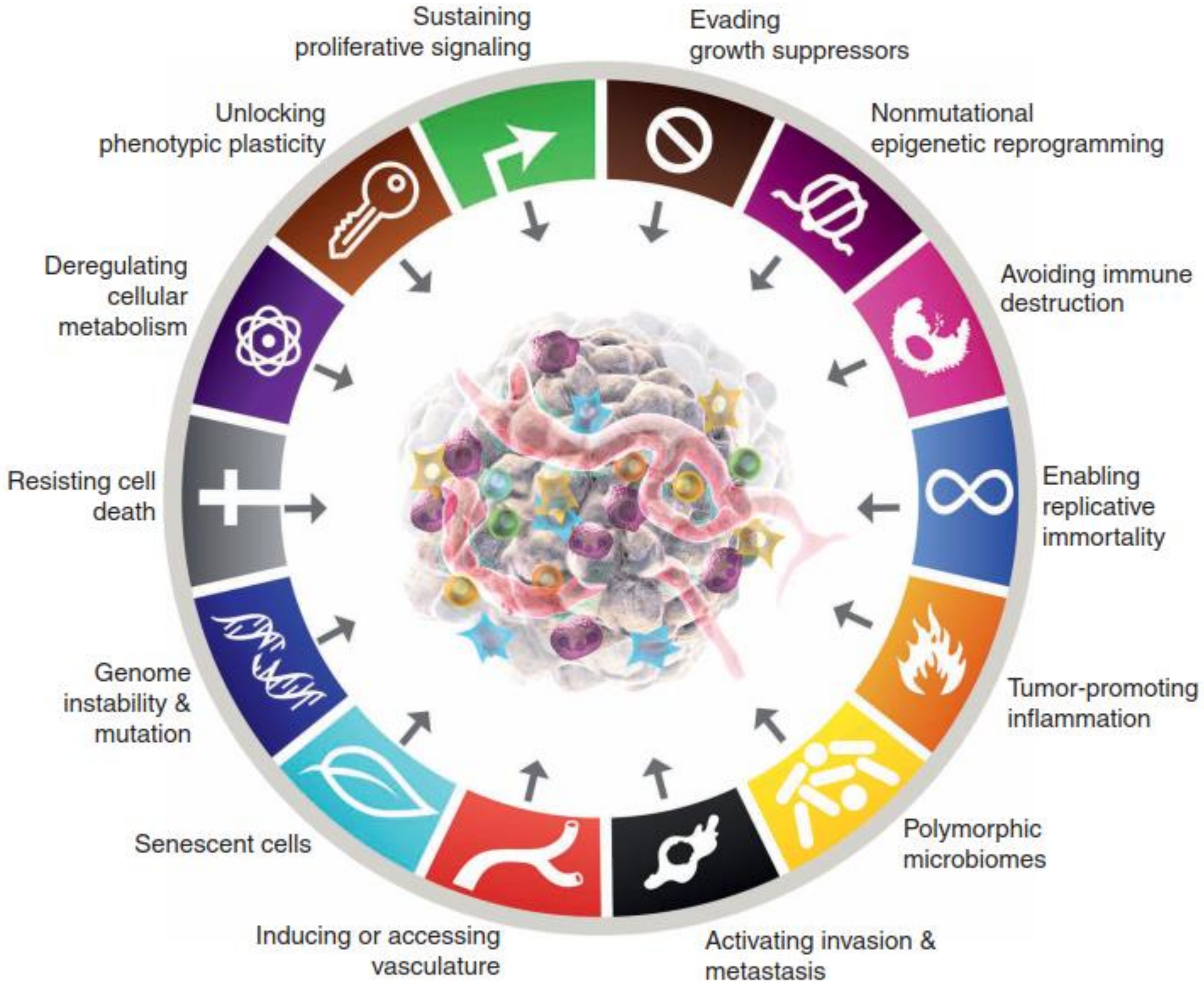
“Microbiomas polimórficos”

Hallmarks do câncer – progressão das pesquisas

2000

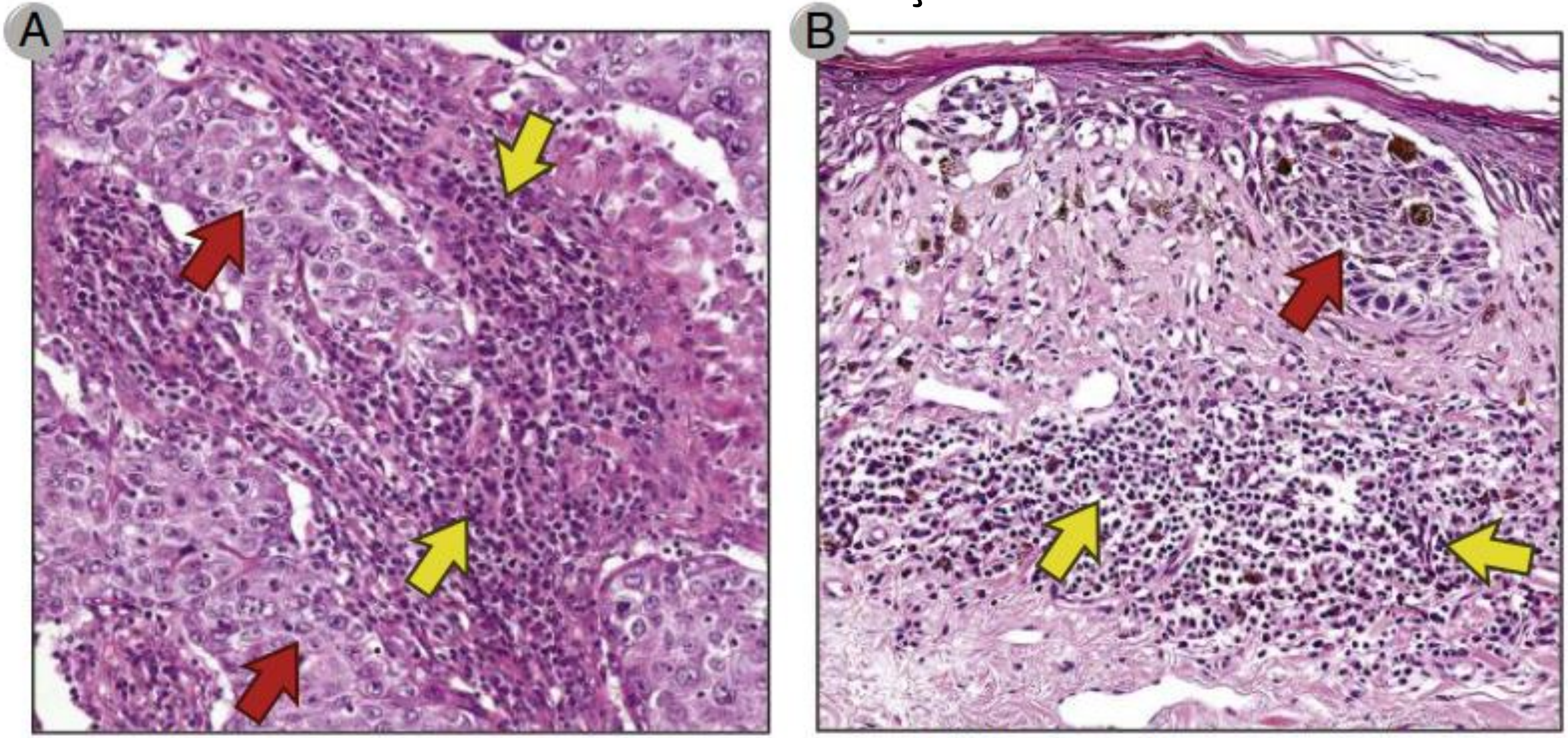


2022



Tumores estimulam respostas imunes

Tumores estimulam respostas imunes adaptativas específicas que podem prevenir ou limitar o crescimento e a disseminação dos canceres



Medullary breast carcinoma   Malignant melanoma of the skin

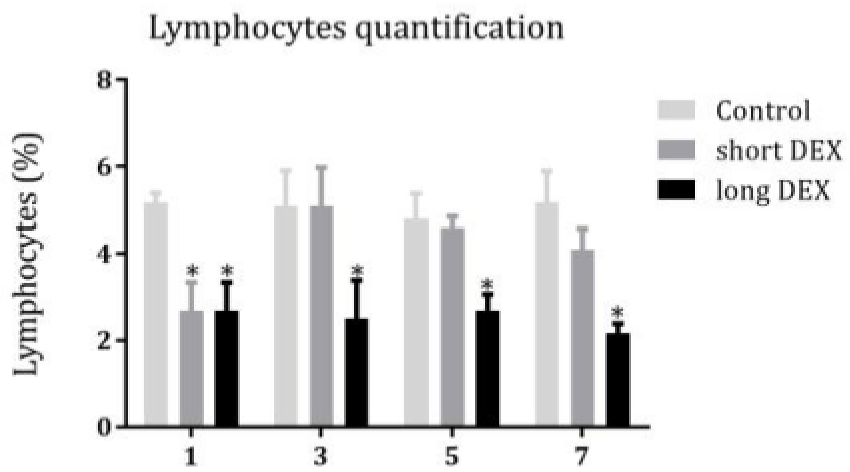
FIGURE 18-1 Lymphocytic inflammation associated with certain tumors. A, Medullary breast carcinoma. **B,** Malignant melanoma. Red arrows indicate malignant cells. Yellow arrows indicate lymphocyte-rich inflammatory infiltrates.

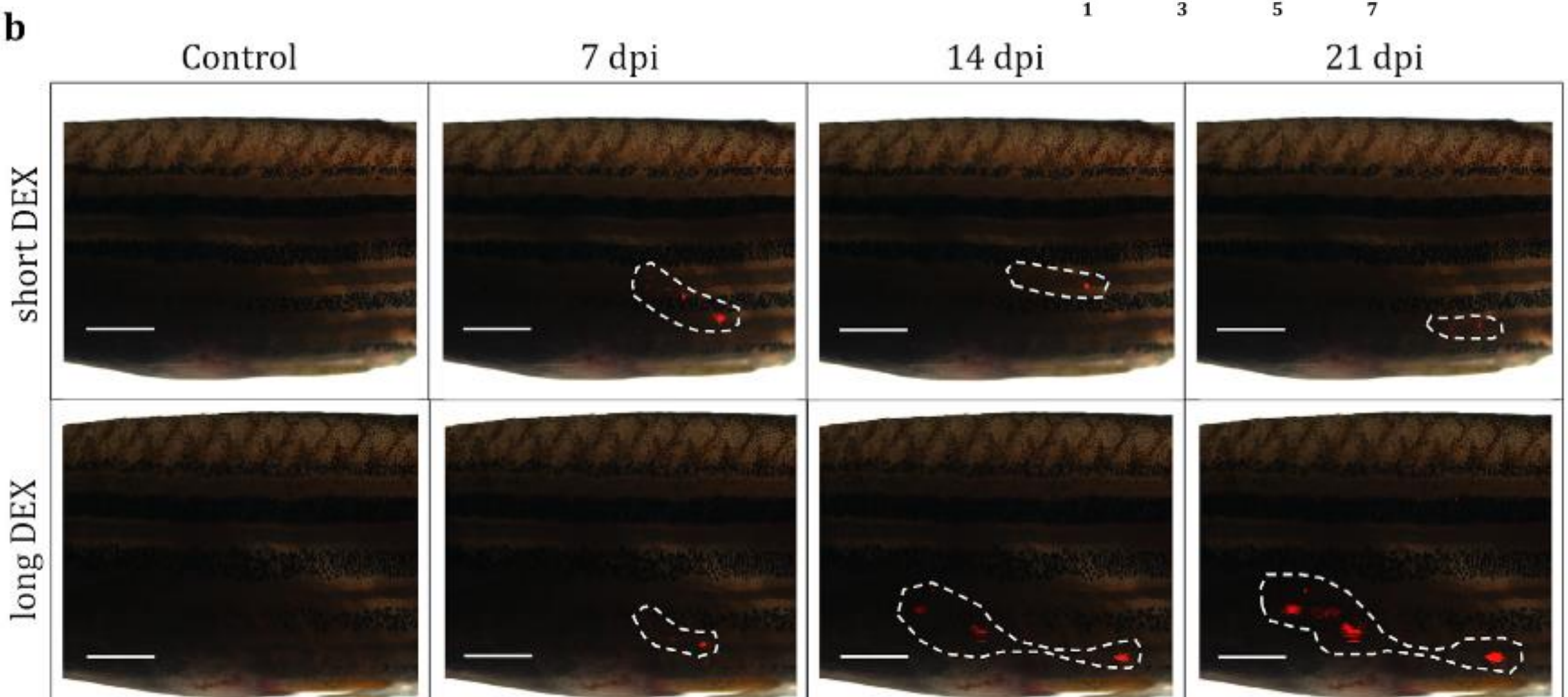
Abbas 8ª edição

Fish and Shellfish Immunology Reports 2 (2021) 100007

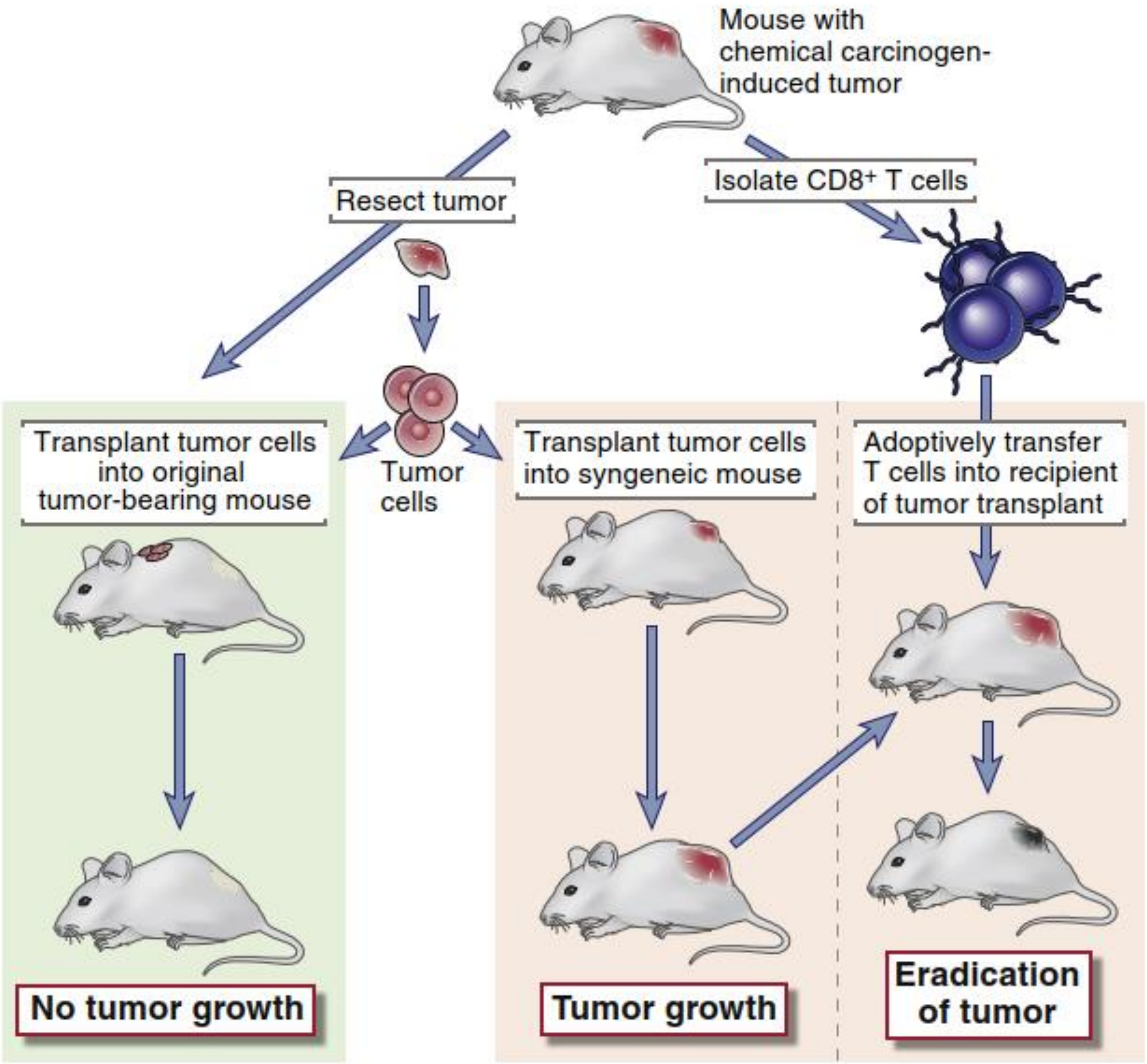
Long-term dexamethasone treatment increases the engraftment efficiency of human breast cancer cells in adult zebrafish

Juliana Moreira Mendonça-Gomes[a,*], Thalita Marcolan Valverde[a,f], Thaís Maria da Mata Martins[f], Ives Charlie-Silva[b], Barbara Nunes Padovani[c], Camila Morales Fénero[c], Eloisa Martins da Silva[c], Rosana Zacarias Domingues[d], Daniela Chemim Melo-Hoyos[e], José Dias Corrêa-Junior[f], Niels Olsen Saraiva Câmara[c], Alfredo Miranda Góes[a,g], Dawidson Assis Gomes[a]





Tumores estimulam respostas imunes



Abbas 8ª edição

Como é produzida uma resposta antitumoral específica?

Como que esses tumores são “enxergados”?

Antígenos

1) Mutação pontual ou deleção gênica
2) Antígenos de genes de células tumorais
3) Antígenos expressos em somente certo estágio do desenvolvimento
4) Antígenos superexpressos em tumores

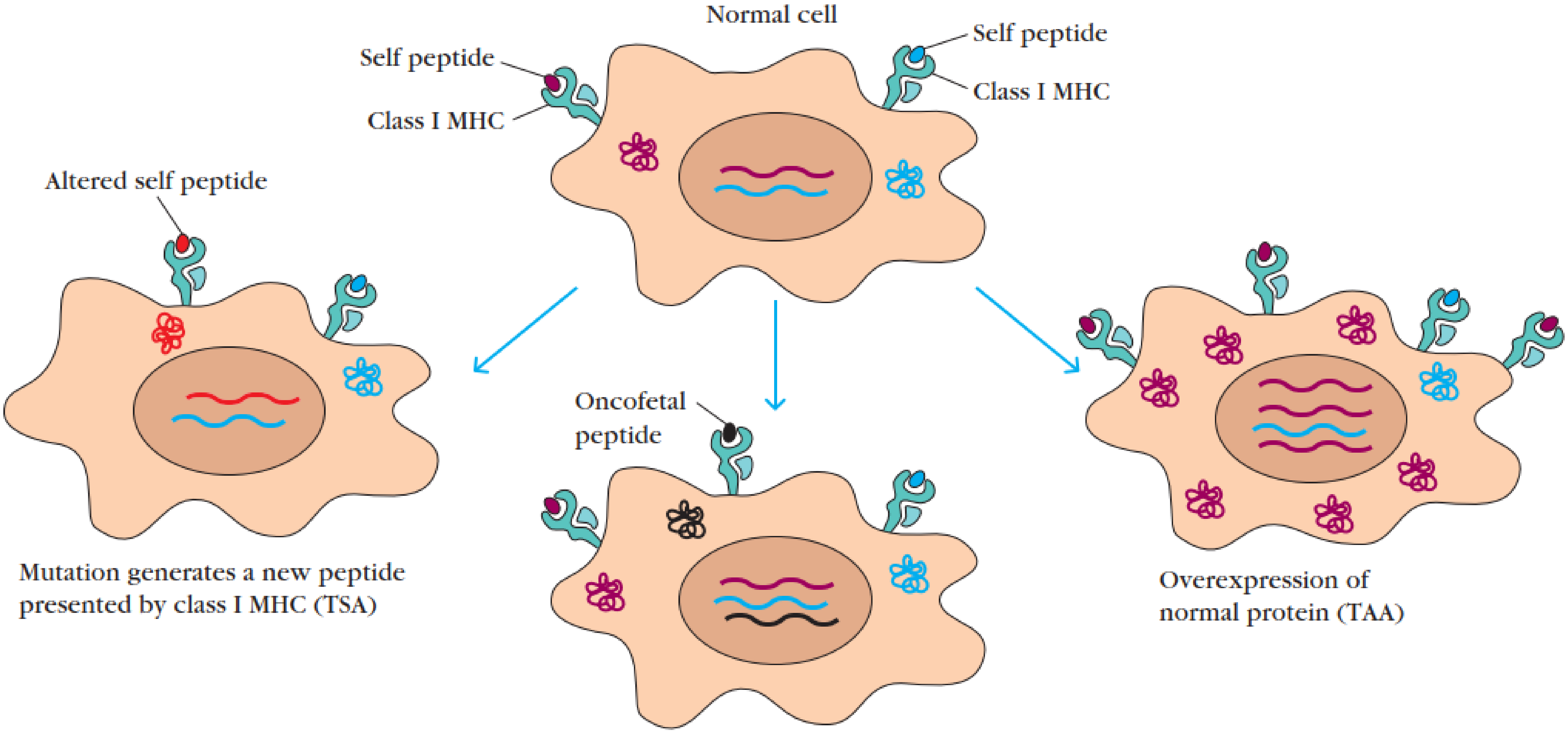
Antígenos TSA

Específicos do tumor

Antígenos TAA

Associados ao tumor

Antígenos específicos (ou associados) ao tumor – TSA e TAA



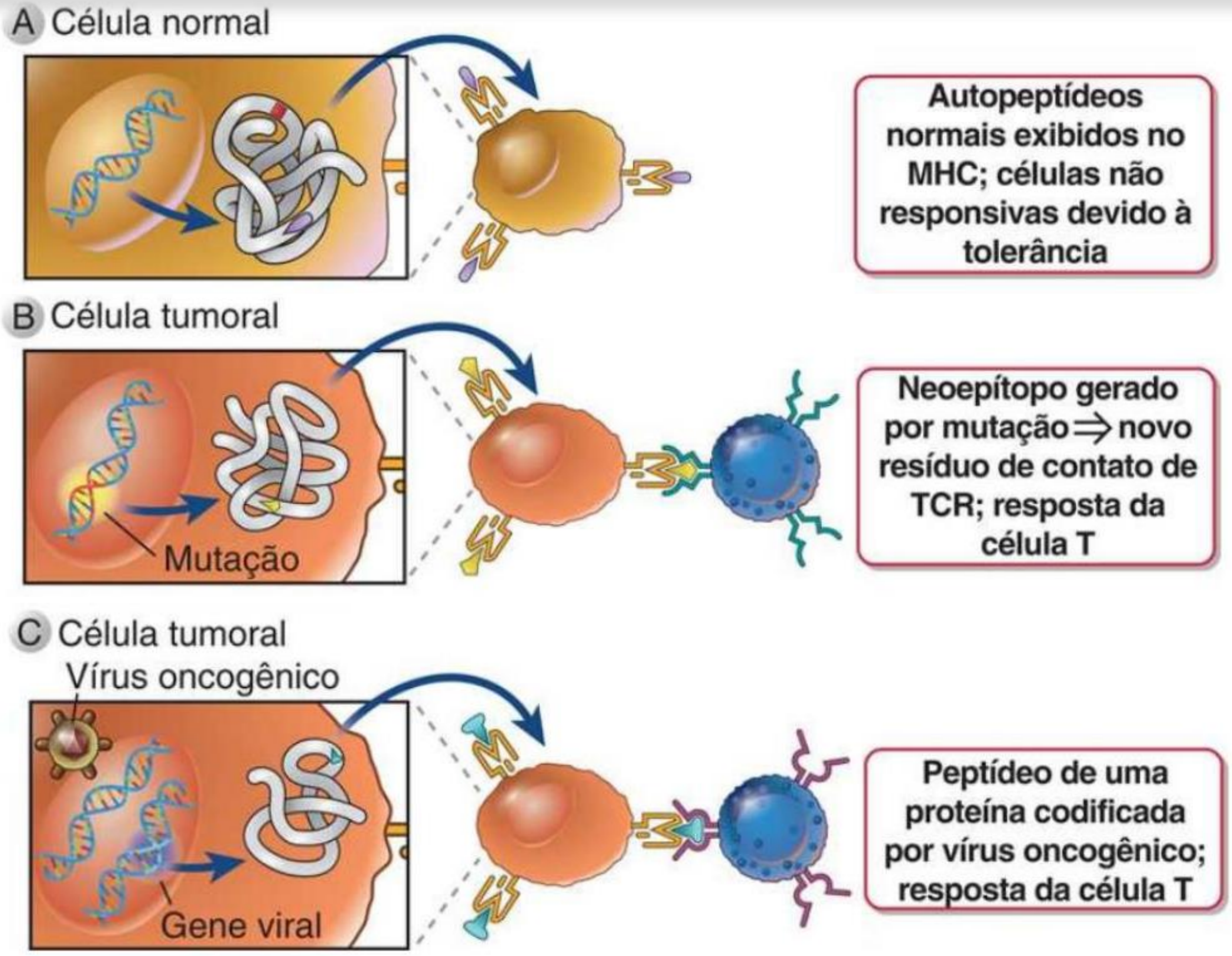
Mutation generates a new peptide presented by class I MHC (TSA)

Inappropriate expression of embryonic gene (TAA)

Overexpression of normal protein (TAA)

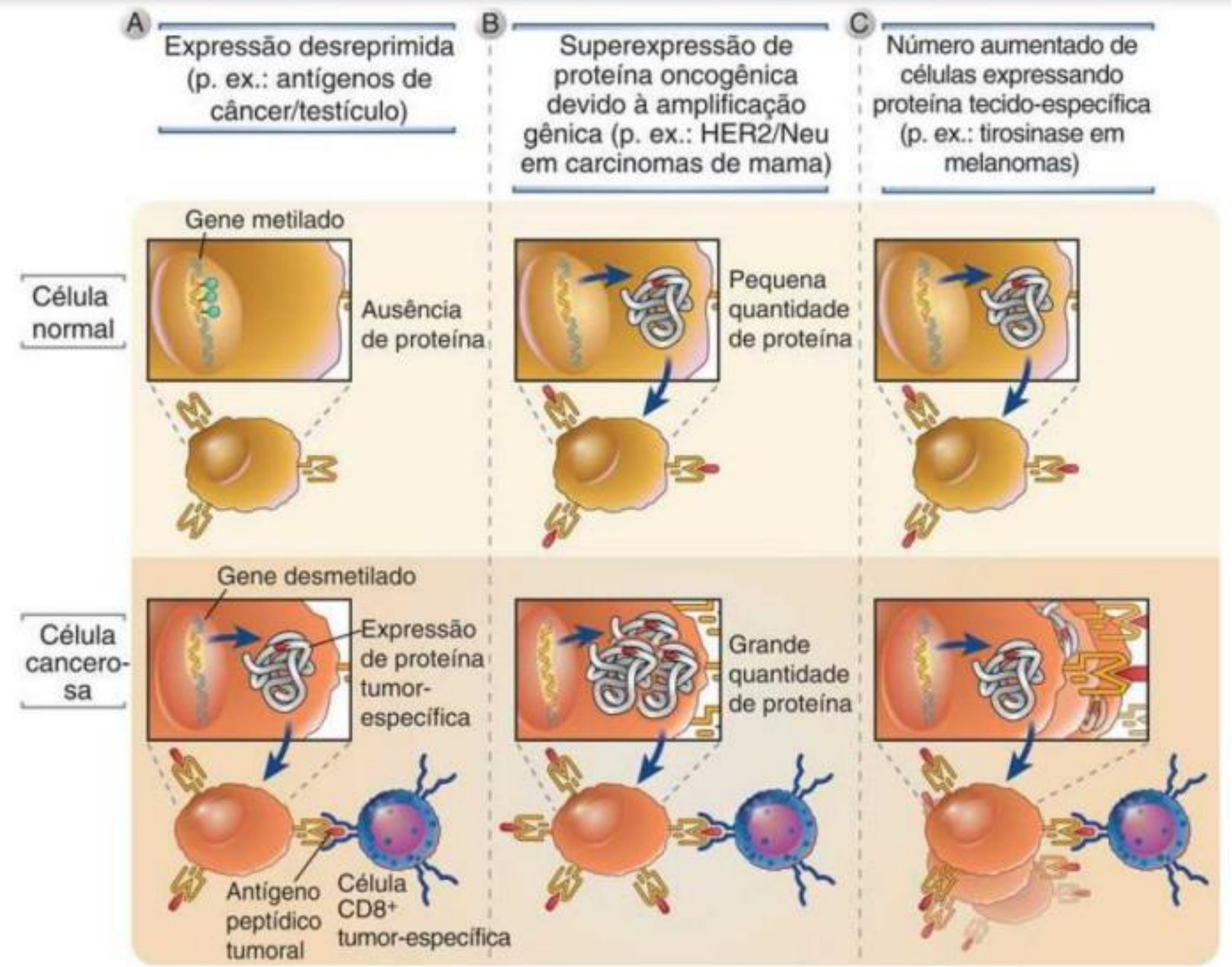
Kuby 7ª edição

TSA – antígenos específicos do tumor



Abbas 9ª edição

TAA – antígenos associados a tumor



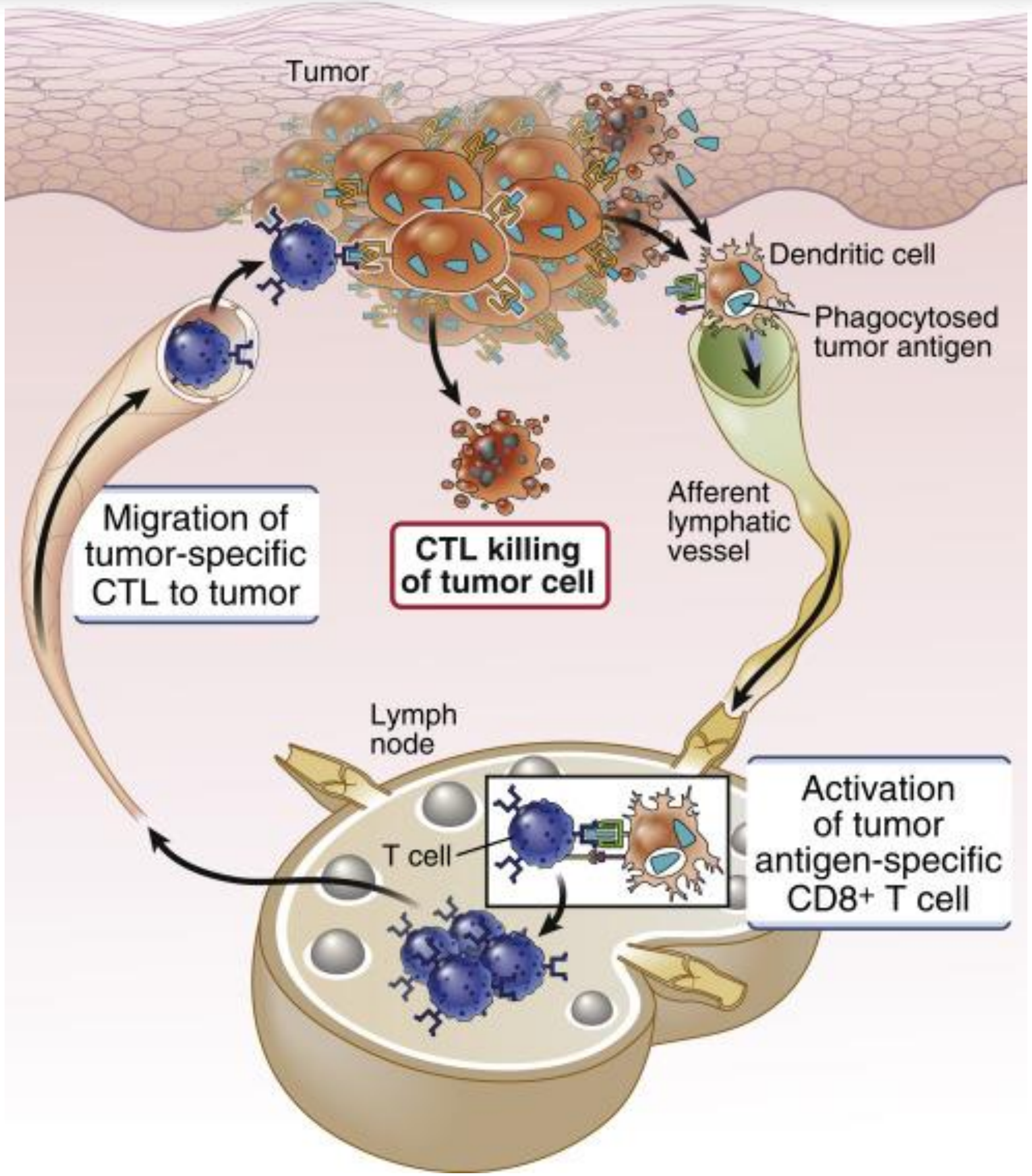
Abbas 9ª edição

Respostas imunes contra tumores

Reparo de DNA – senescência ou apoptose

Sinais ambientais – interrupção do crescimento ou apoptose

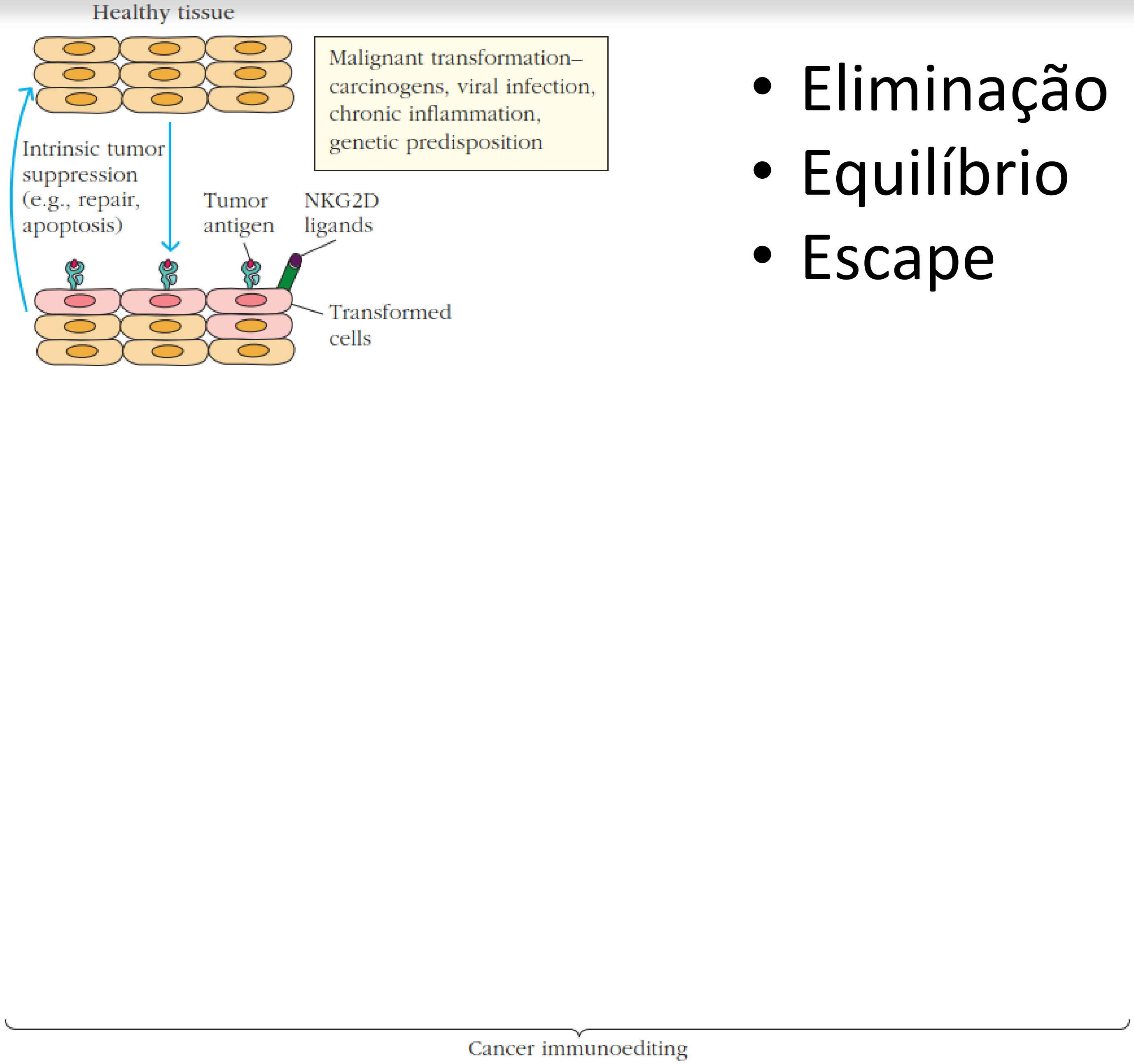
Sistema imunológico!



- Células T
- Células B
- Células NK
- IFNγ

Abbas 9ª edição

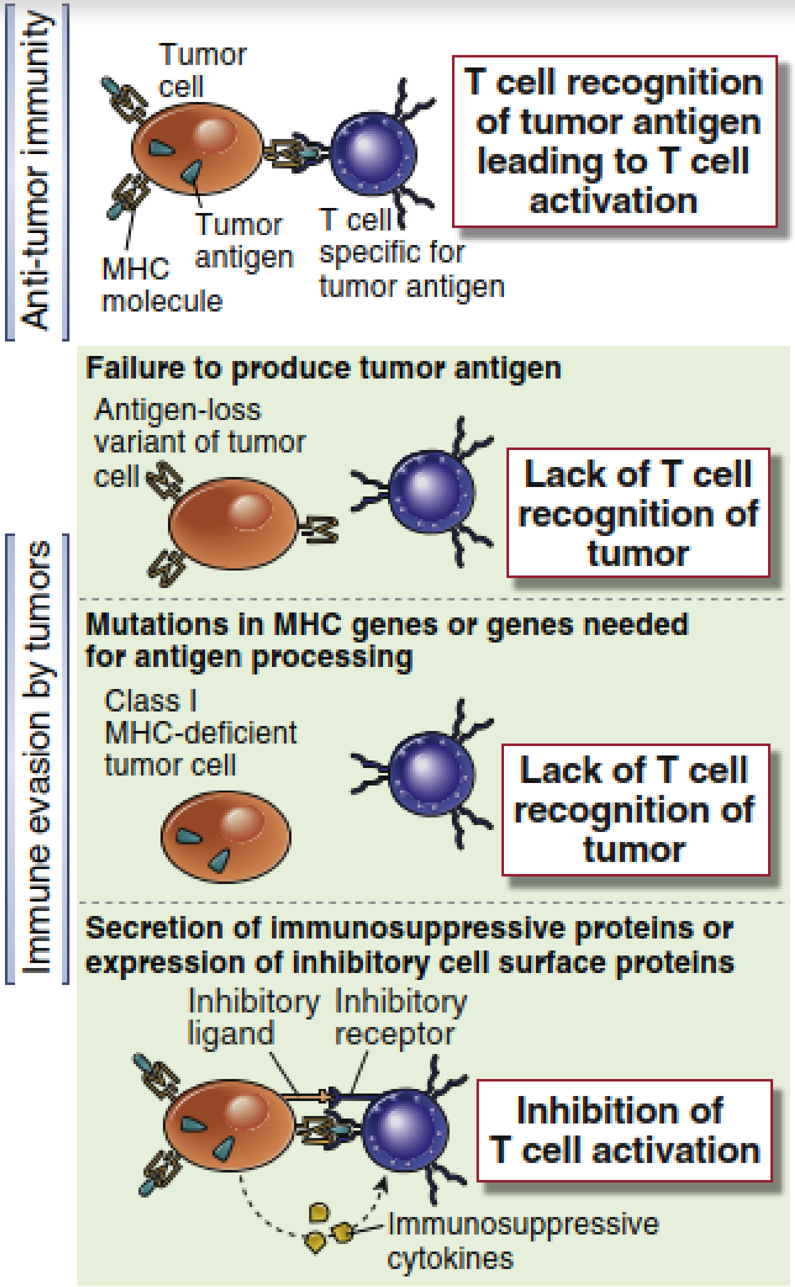
Os três estágios da imunoedição do câncer



- Eliminação
- Equilíbrio
- Escape

Kuby 7ª edição

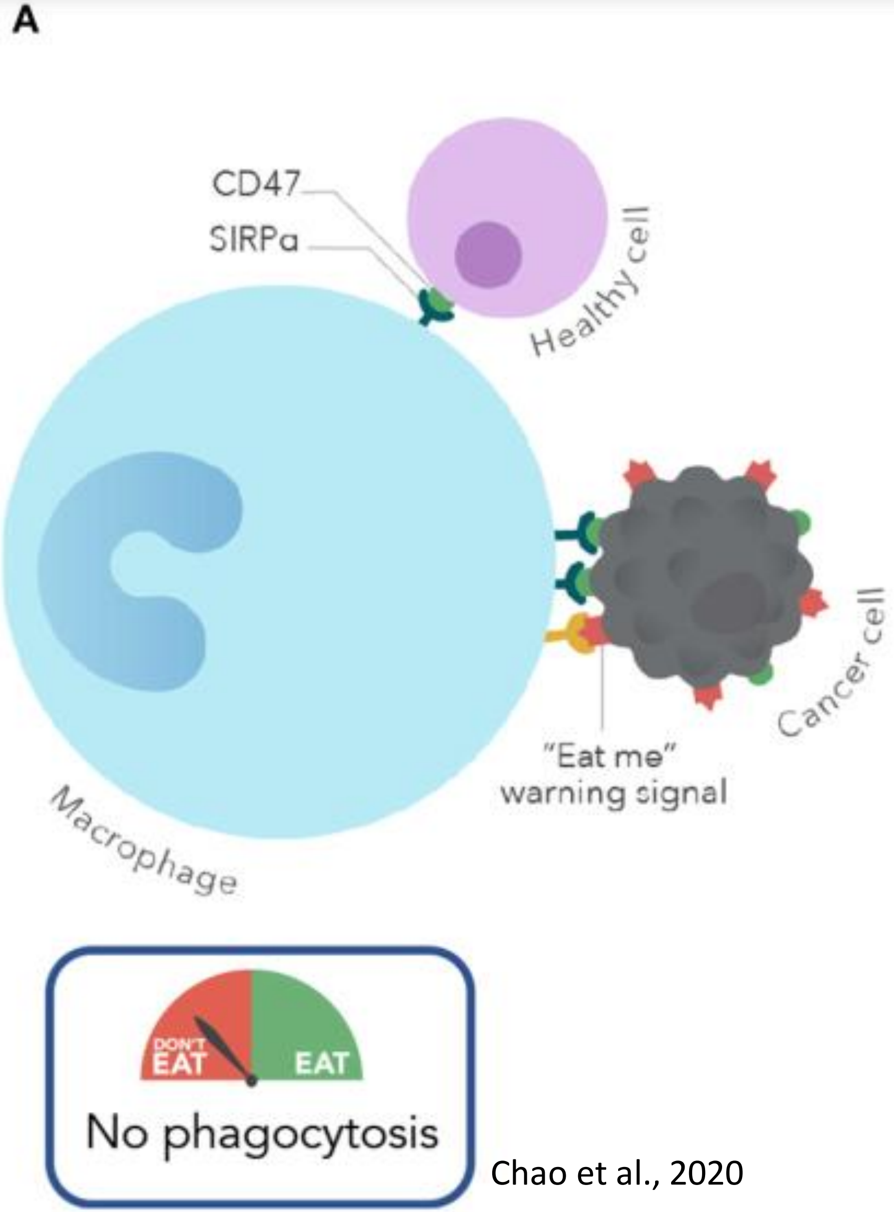
Evasão do sistema imune



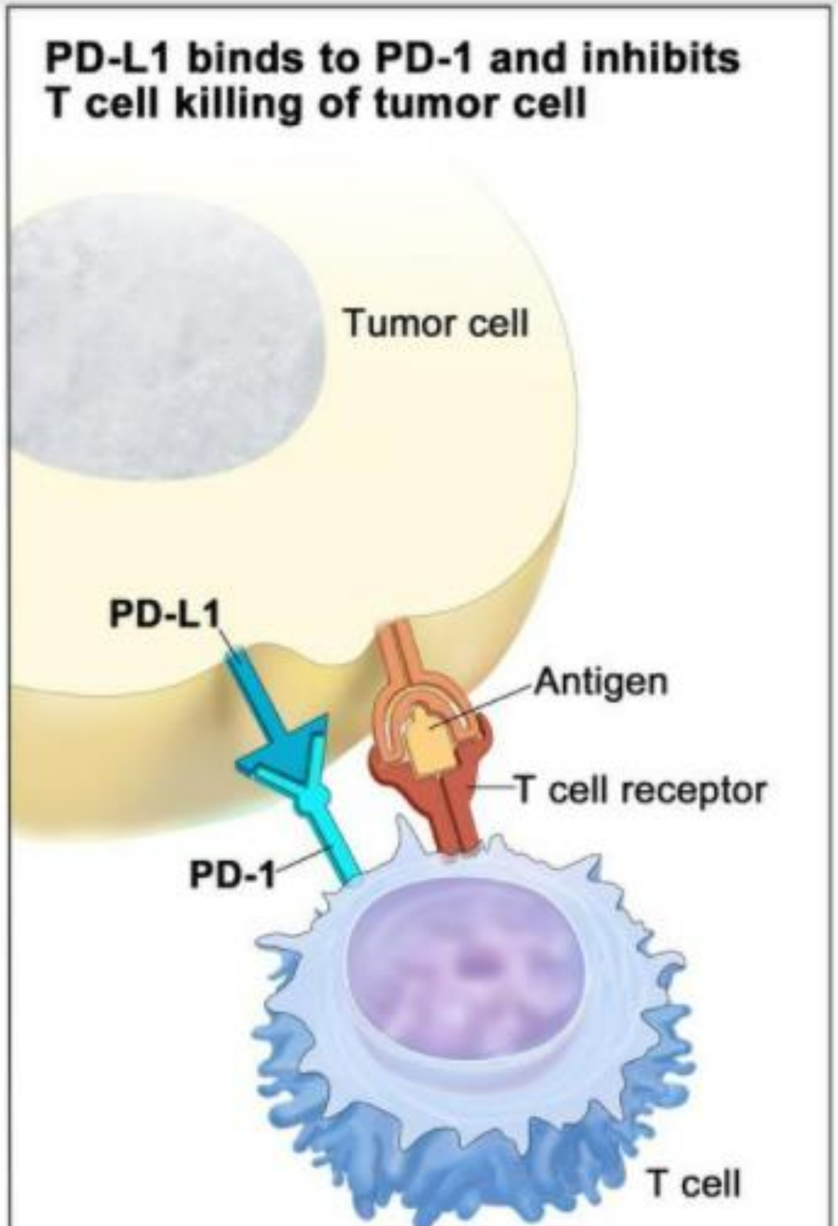
- Inibição ativa da resposta imune
- Perda dos antígenos ou moléculas de MHC que dirigem essas respostas

Abbas 8ª edição

Evasão do sistema imune

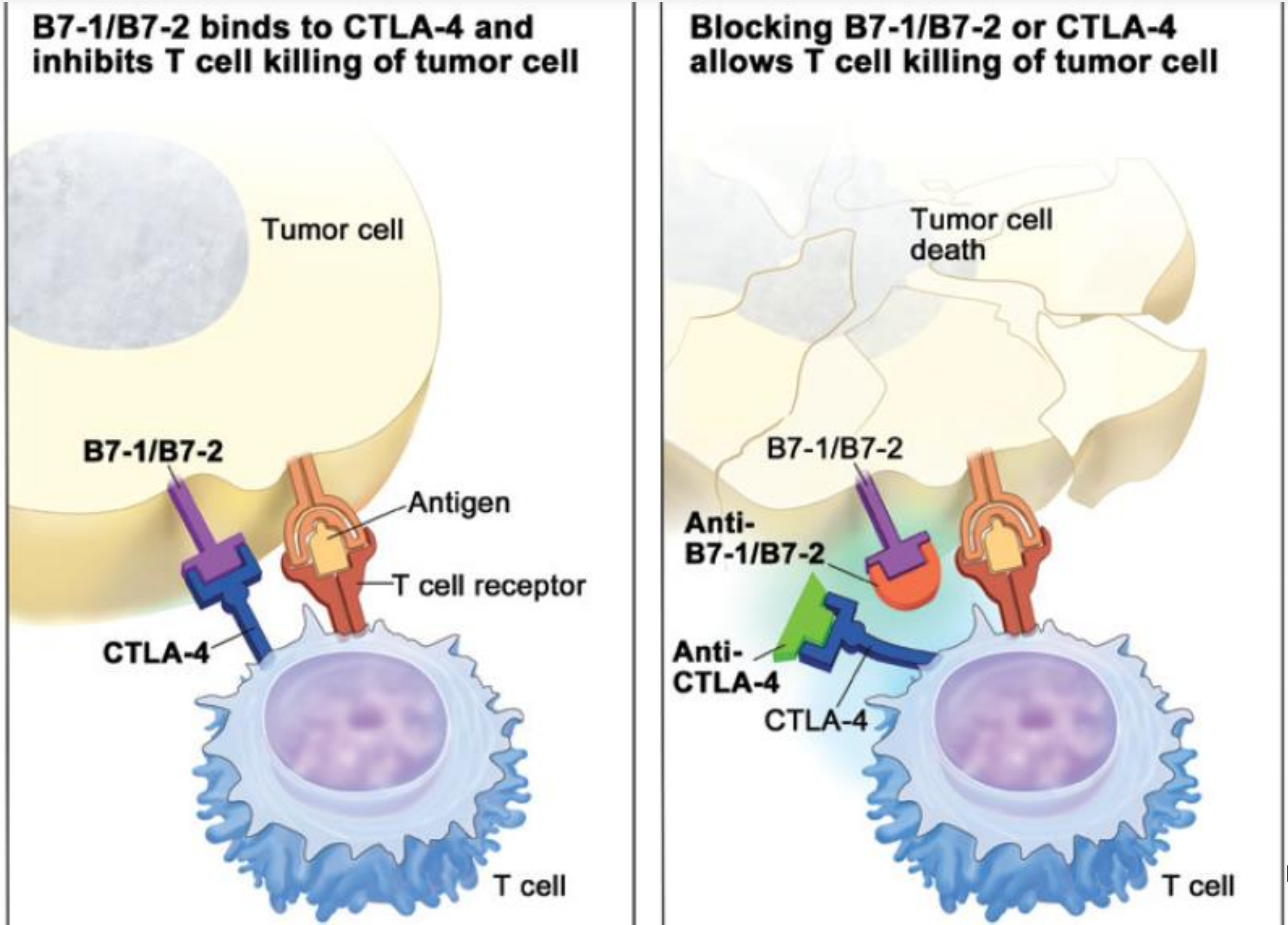


Chao et al., 2020



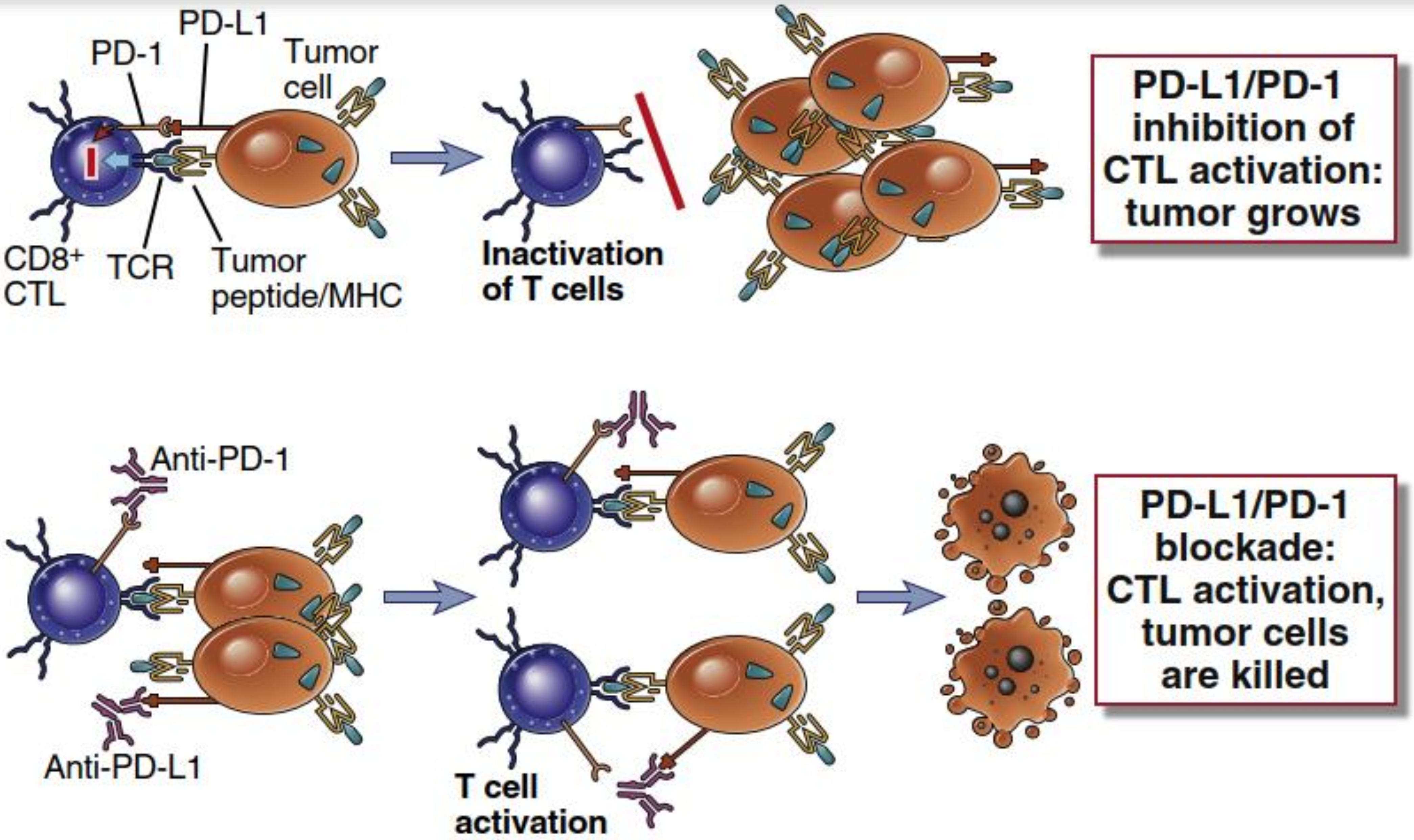
Credit: National Cancer Institute

Evasão do sistema imune



Eno, 2017

Bloqueio de pontos de controle



Abbas 8ª ediçao

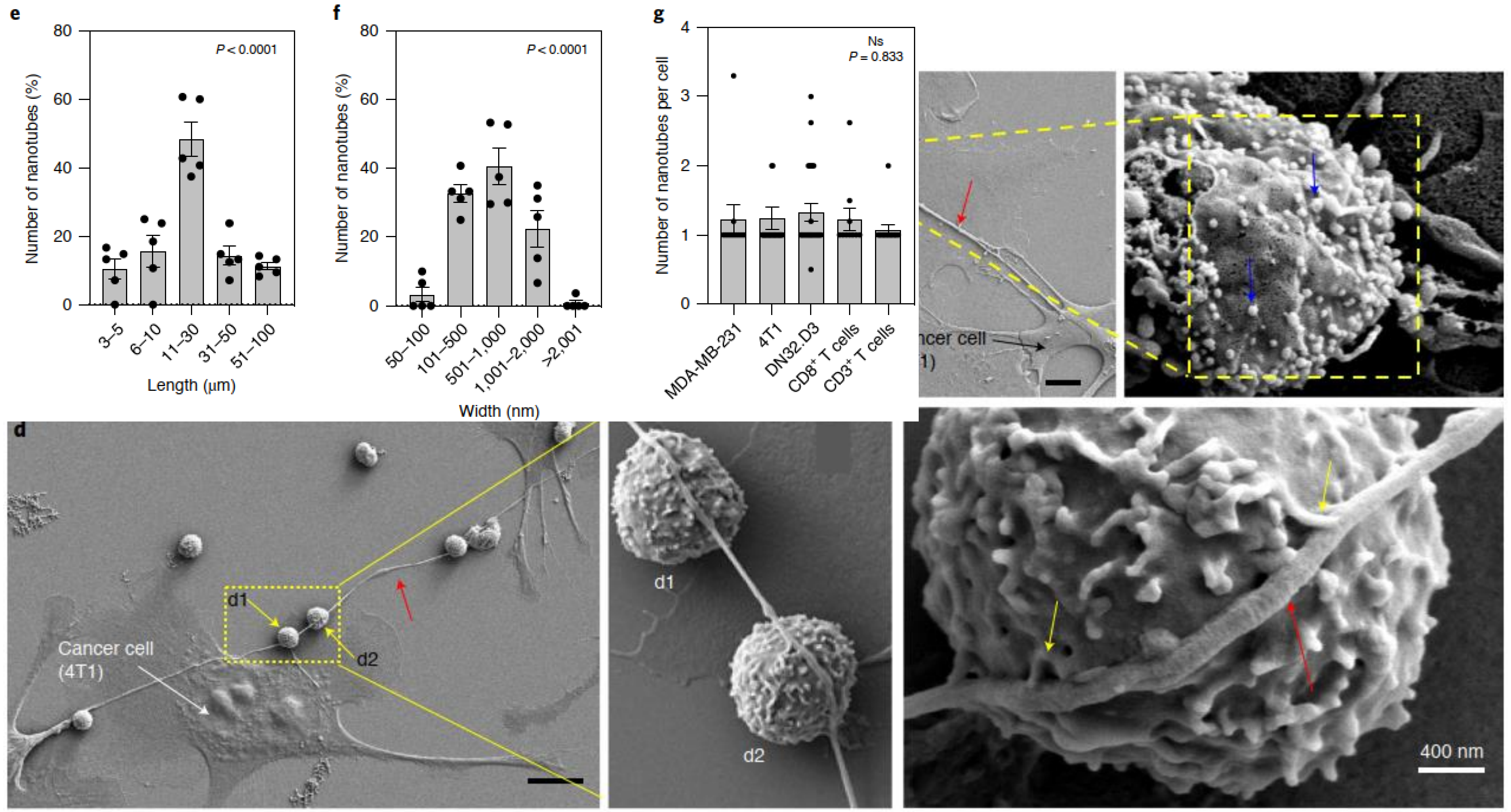
ARTICLES
https://doi.org/10.1038/s41565-021-01000-4
nature nanotechnology

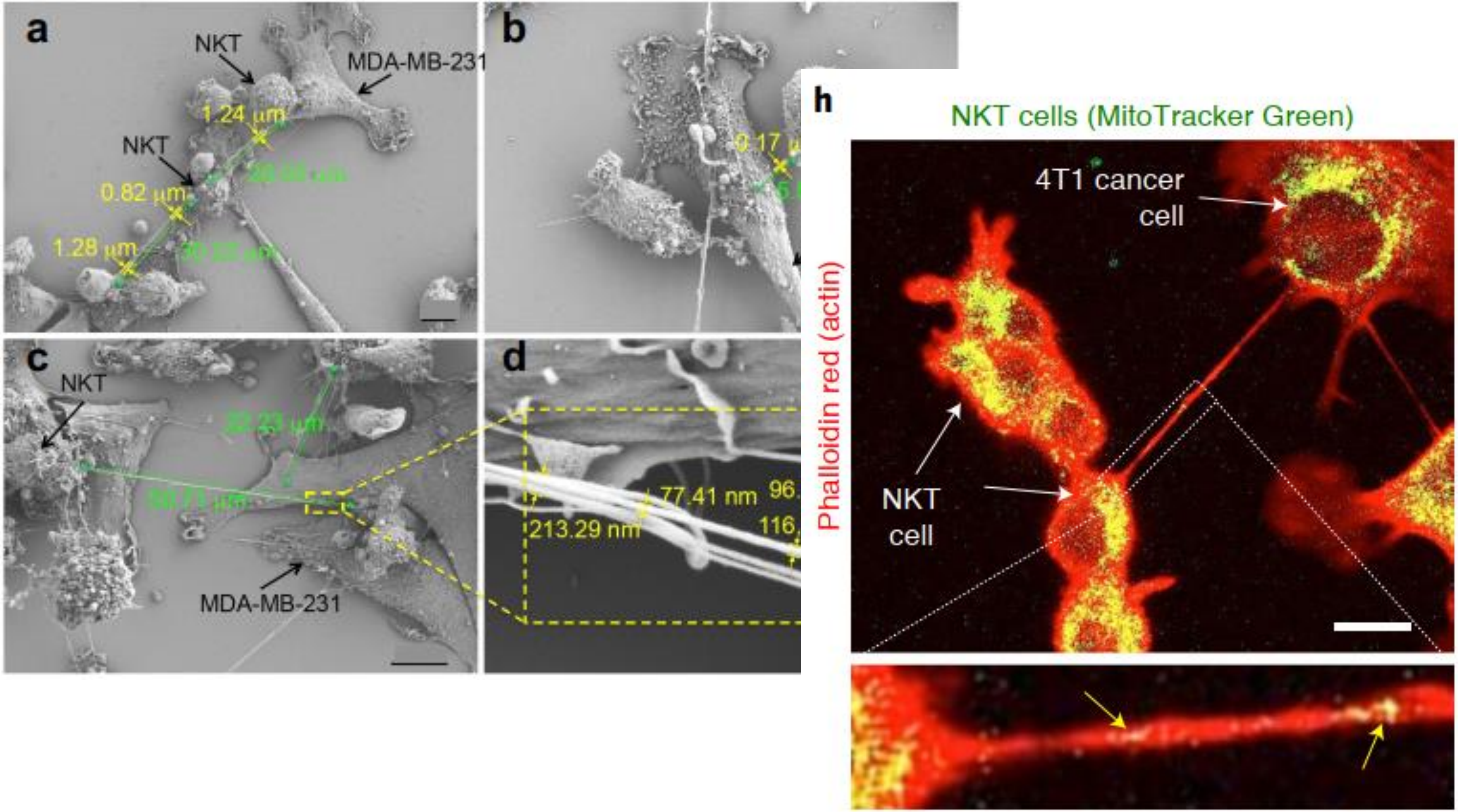
Check for updates

Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells

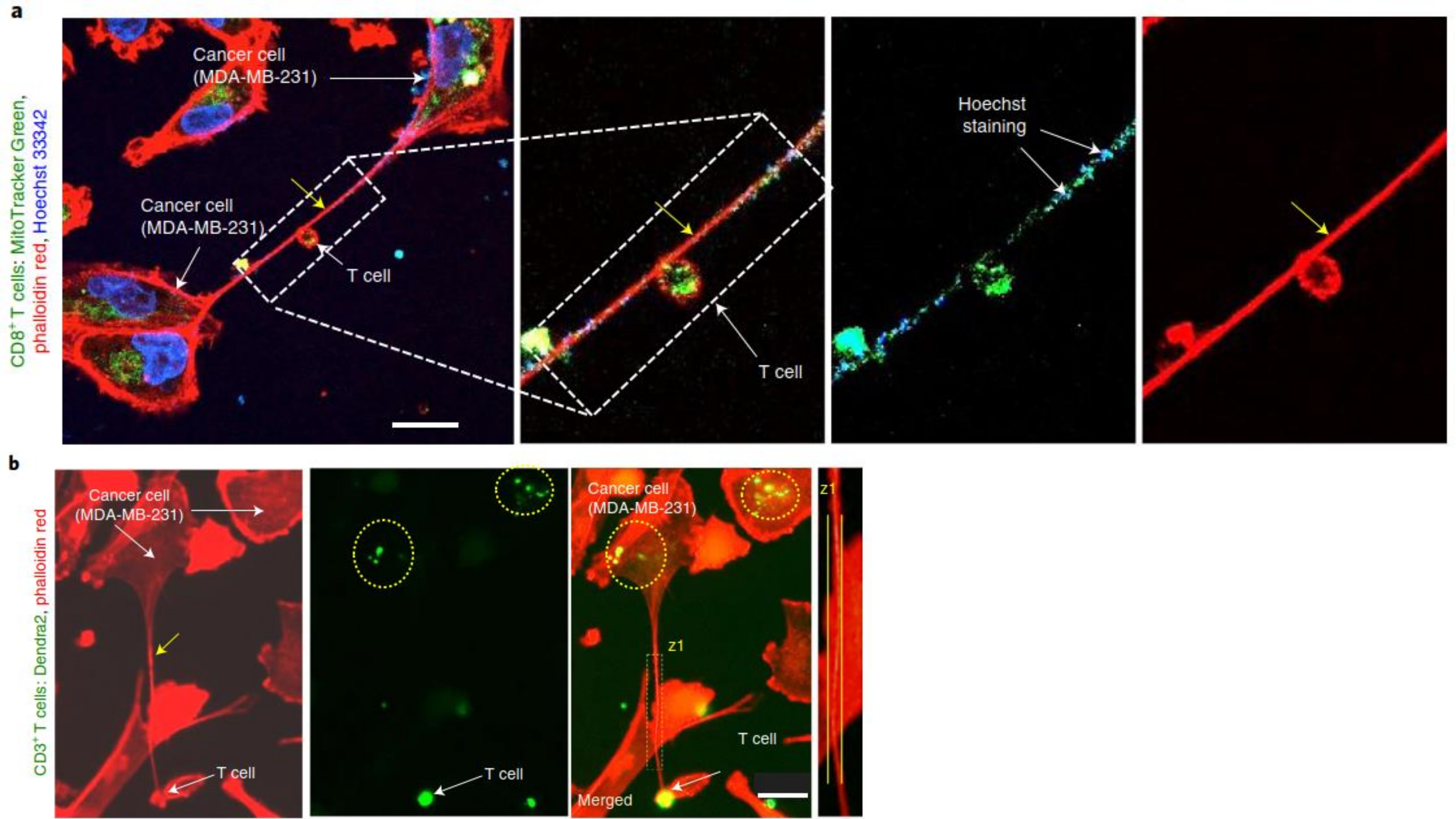
Tanmoy Saha[1,2], Chinmayee Dash[1,2], Ruparoshni Jayabalan[1,2], Sachin Khiste[1,2], Arpita Kulkarni[1], Kiran Kurmi[3], Jayanta Mondal[1,2], Pradip K. Majumder[4], Aditya Bardia[5], Hae Lin Jang[1] ✉ and Shiladitya Sengupta[1,2,6] ✉

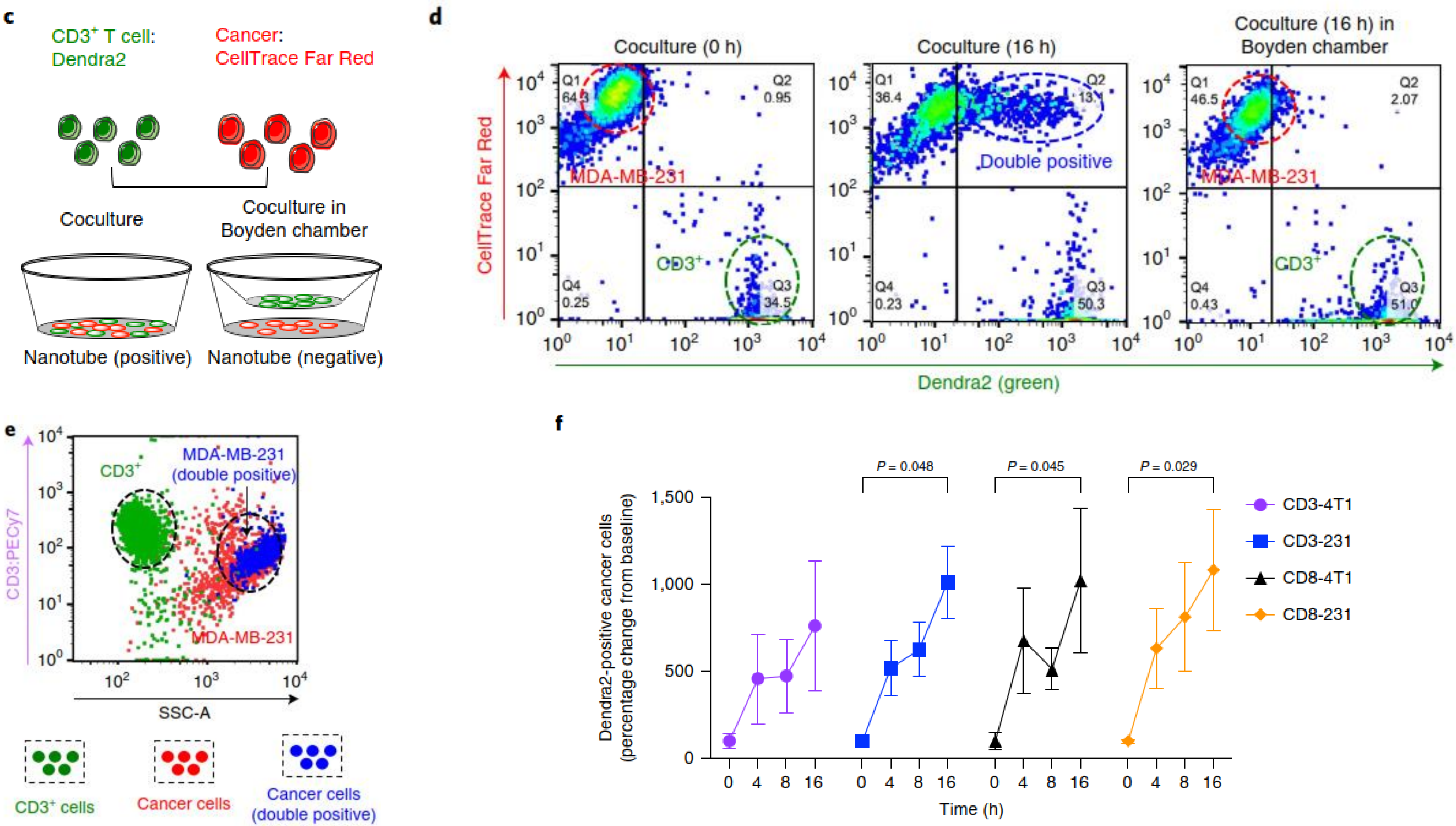
Juliana M M Gomes

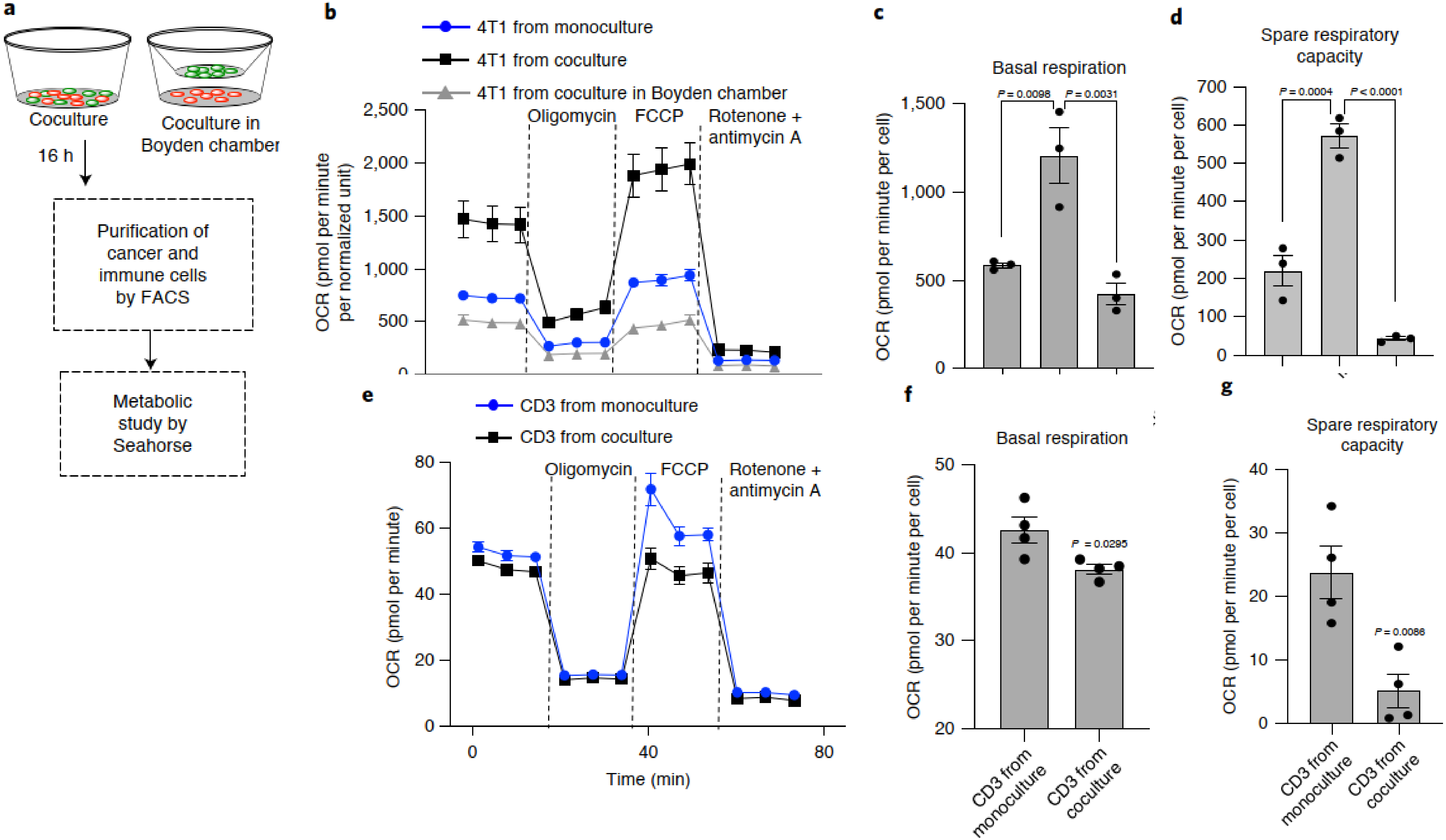

e
P < 0.0001
Number of nanotubes (%)
0
20
40
60
80
3–5
6–10
11–30
31–50
51–100
Length (µm)
f
P < 0.0001
Number of nanotubes (%)
0
20
40
60
80
50–100
101–500
501–1,000
1,001–2,000
>2,001
Width (nm)
g
Ns
P = 0.833
Number of nanotubes per cell
0
1
2
3
4
MDA-MB-231
4T1
DN32.D3
CD8+ T cells
CD3+ T cells
ncer cell
1)
d
d1
d2
Cancer cell
(4T1)
d1
d2
400 nm



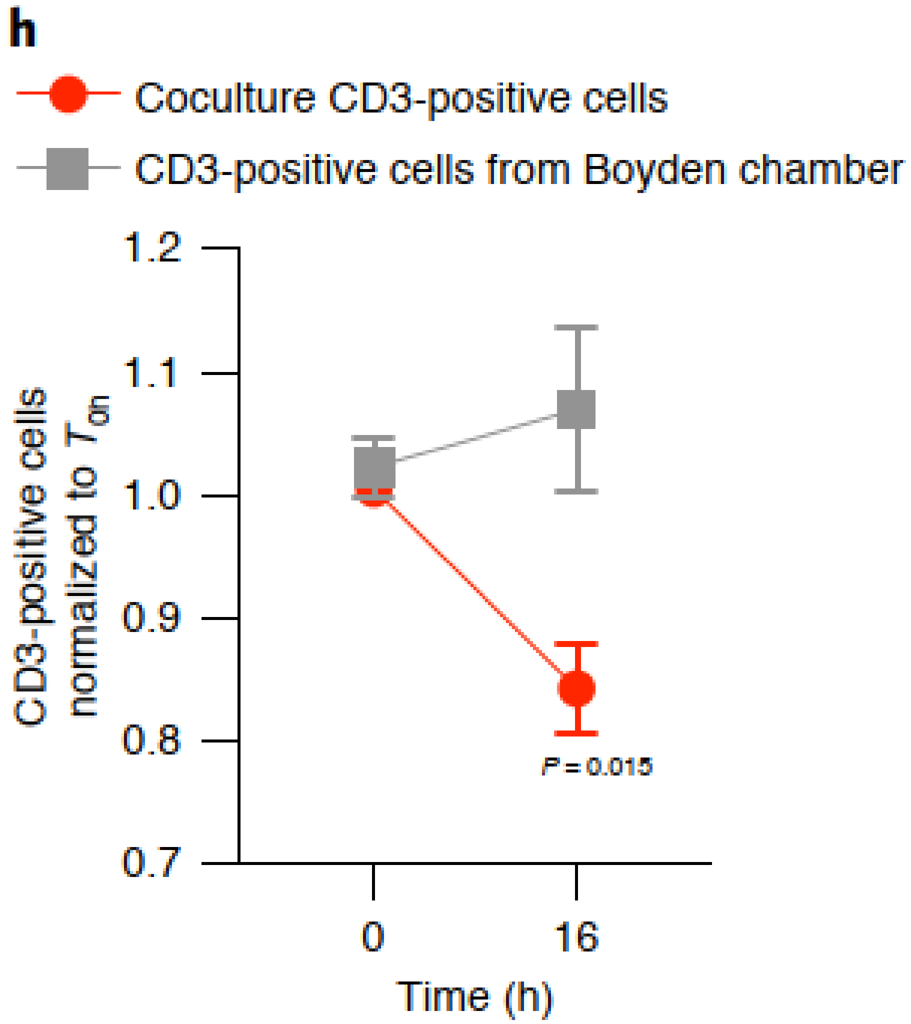
a
NKT
MDA-MB-231
1.24 µm
NKT
0.82 µm
1.28 µm
b
c
NKT
MDA-MB-231
d
77.41 nm
213.29 nm
h
NKT cells (MitoTracker Green)
Phalloidin red (actin)
4T1 cancer cell
NKT cell

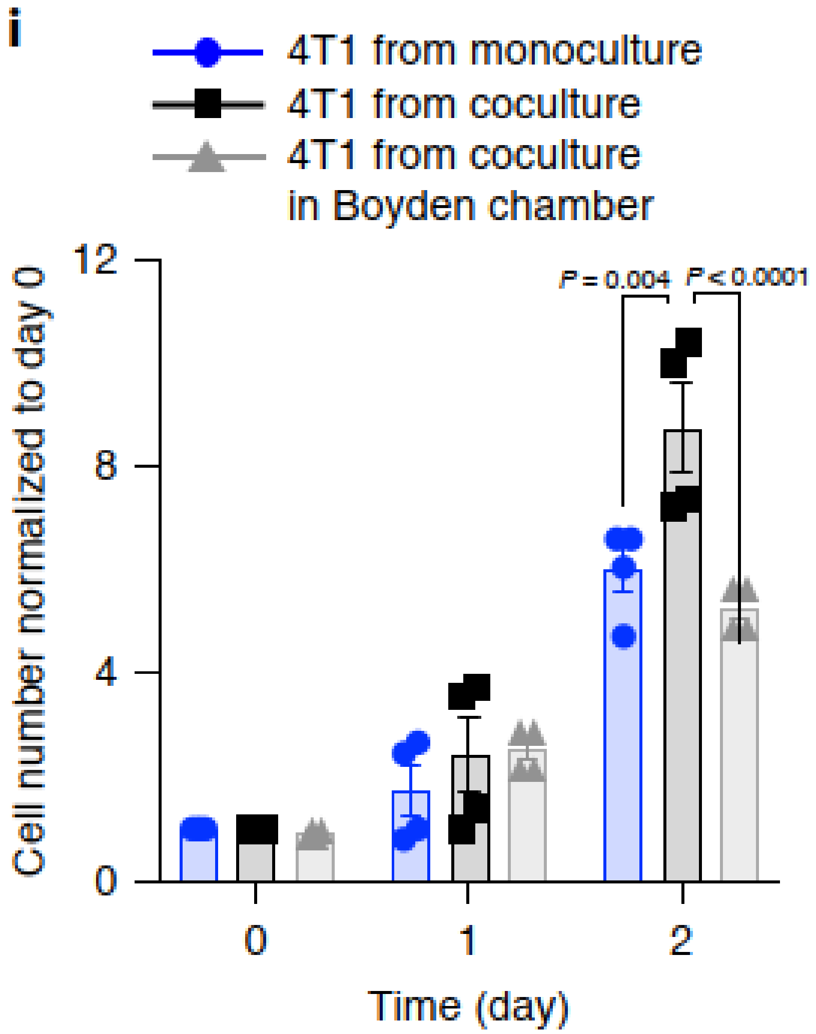

a
CD8+ T cells: MitoTracker Green, phalloidin red, Hoechst 33342
Cancer cell (MDA-MB-231)
Cancer cell (MDA-MB-231)
T cell
T cell
Hoechst staining
b
CD3+ T cells: Dendra2, phalloidin red
Cancer cell (MDA-MB-231)
T cell
T cell
Cancer cell (MDA-MB-231)
z1
T cell
Merged
z1

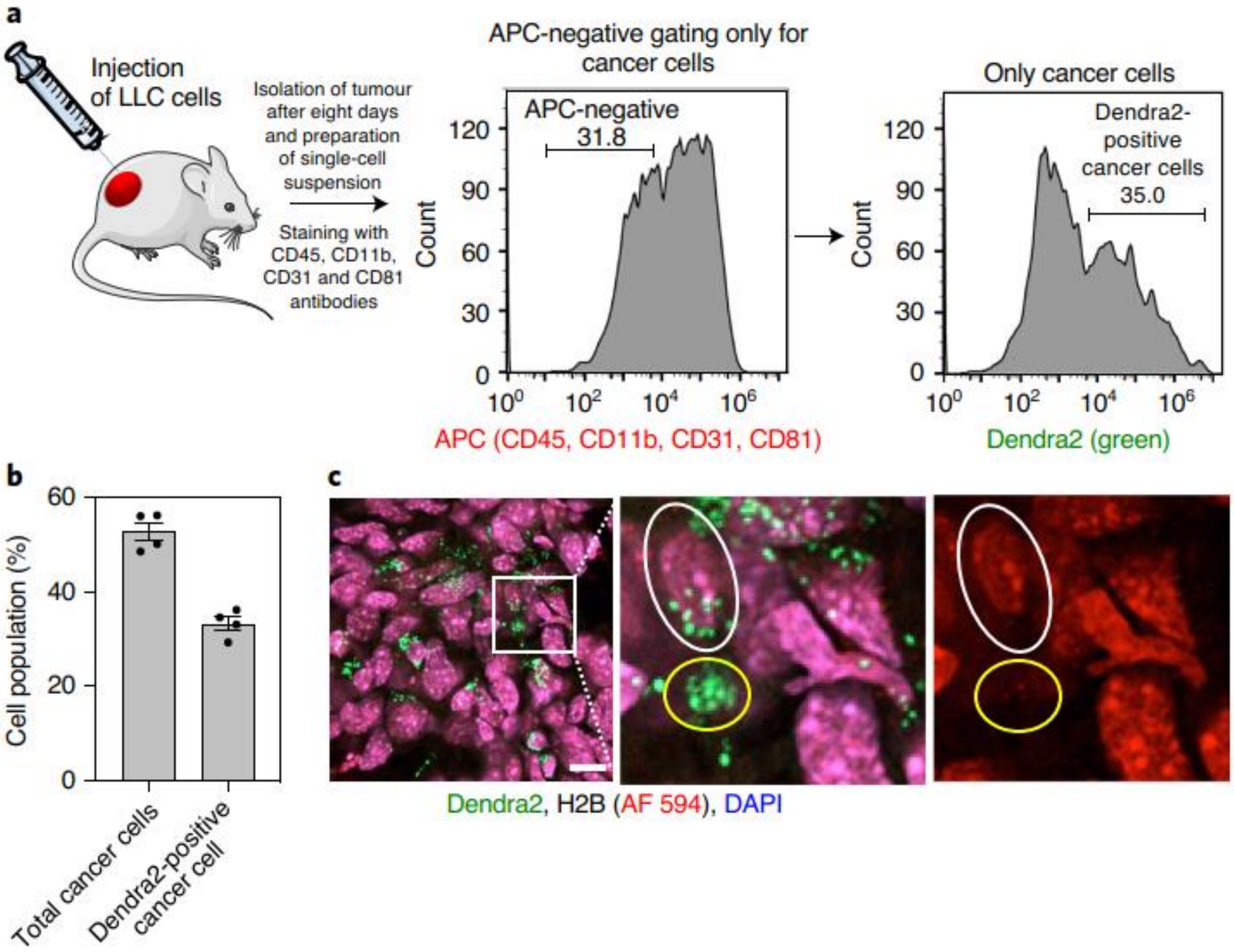

c
CD3+ T cell:
Dendra2
Cancer:
CellTrace Far Red
Coculture
Coculture in
Boyden chamber
Nanotube (positive)
Nanotube (negative)
d
Coculture (0 h)
Coculture (16 h)
Coculture (16 h) in
Boyden chamber
CellTrace Far Red
Dendra2 (green)
Q1
Q2
Q3
Q4
64.3
0.95
34.5
0.25
36.4
13.1
50.3
0.23
46.5
2.07
51.0
0.43
MDA-MB-231
CD3+
Double positive
e
CD3:PECy7
SSC-A
CD3+
MDA-MB-231
(double positive)
MDA-MB-231
CD3+ cells
Cancer cells
Cancer cells
(double positive)
f
Dendra2-positive cancer cells
(percentage change from baseline)
Time (h)
P = 0.048
P = 0.045
P = 0.029
CD3-4T1
CD3-231
CD8-4T1
CD8-231



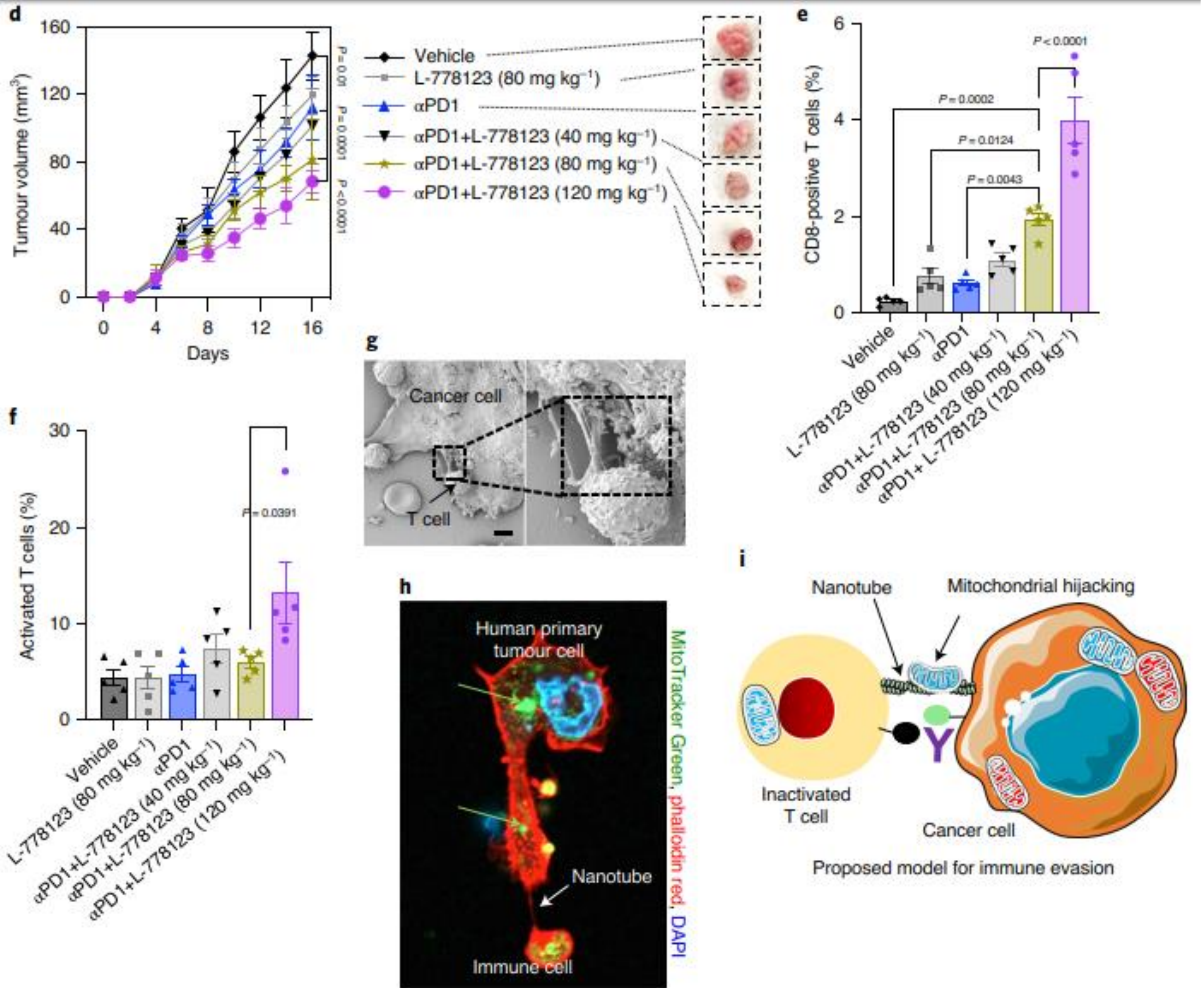
a
Coculture
Coculture in Boyden chamber
16 h
Purification of cancer and immune cells by FACS
Metabolic study by Seahorse
b
4T1 from monoculture
4T1 from coculture
4T1 from coculture in Boyden chamber
Oligomycin
FCCP
Rotenone + antimycin A
OCR (pmol per minute per normalized unit)
2,500
2,000
1,500
1,000
500
0
c
Basal respiration
P = 0.0098
P = 0.0031
OCR (pmol per minute per cell)
1,500
1,000
500
0
d
Spare respiratory capacity
P = 0.0004
P < 0.0001
OCR (pmol per minute per cell)
700
600
500
400
300
200
100
0
e
CD3 from monoculture
CD3 from coculture
Oligomycin
FCCP
Rotenone + antimycin A
OCR (pmol per minute)
80
60
40
20
0
0
40
80
Time (min)
f
Basal respiration
P = 0.0295
OCR (pmol per minute per cell)
50
40
30
20
CD3 from monoculture
CD3 from coculture
g
Spare respiratory capacity
P = 0.0086
OCR (pmol per minute per cell)
40
30
20
10
0
CD3 from monoculture
CD3 from coculture


h
Coculture CD3-positive cells
CD3-positive cells from Boyden chamber
CD3-positive cells normalized to T_{0h}
1.2
1.1
1.0
0.9
0.8
0.7
P = 0.015
0
16
Time (h)

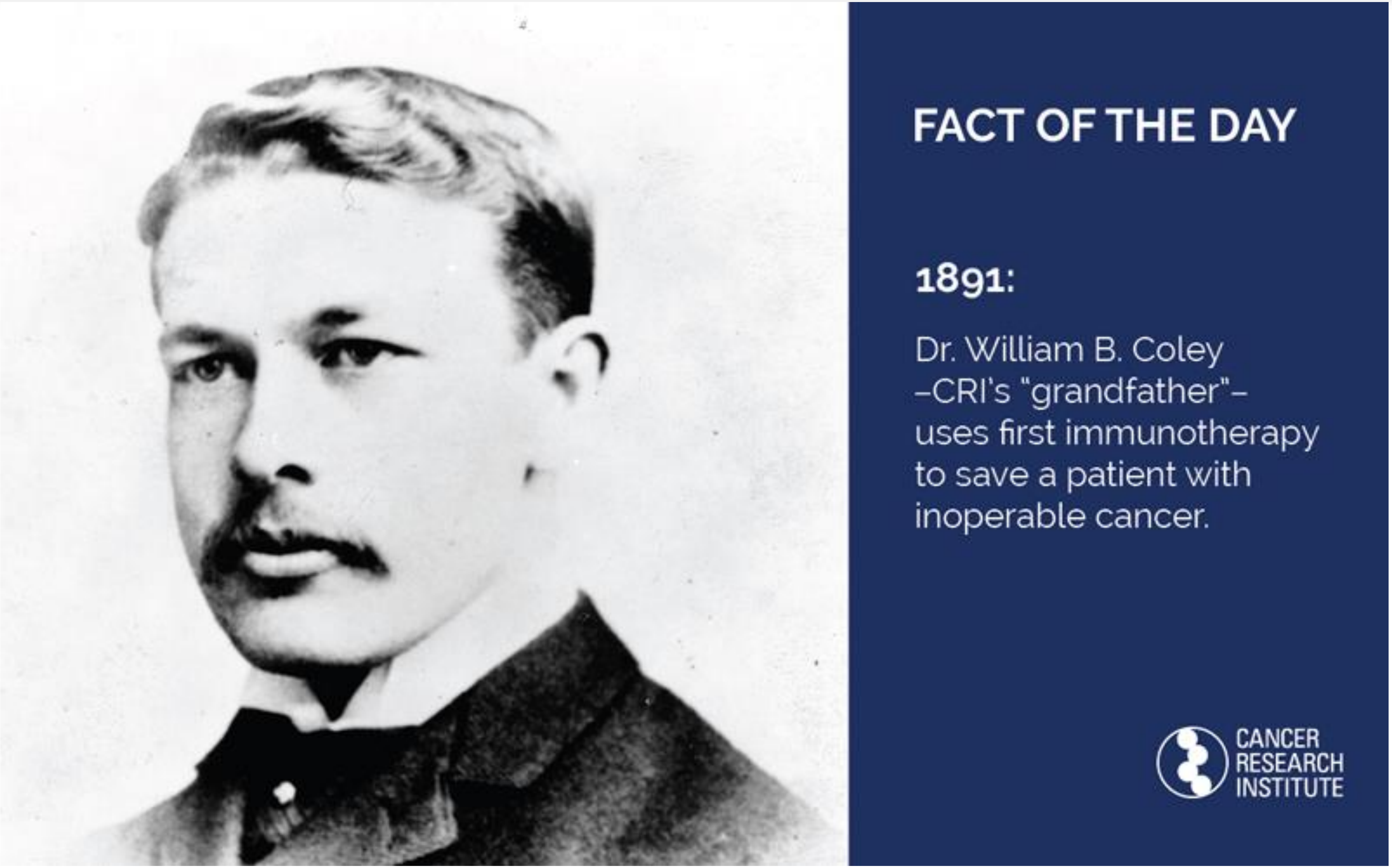

i
4T1 from monoculture
4T1 from coculture
4T1 from coculture in Boyden chamber
Cell number normalized to day 0
12
8
4
0
P = 0.004
P < 0.0001
0
1
2
Time (day)



a
Injection of LLC cells
Isolation of tumour after eight days and preparation of single-cell suspension
Staining with CD45, CD11b, CD31 and CD81 antibodies
APC-negative gating only for cancer cells
APC-negative
31.8
Count
120
90
60
30
0
10^0
10^2
10^4
10^6
APC (CD45, CD11b, CD31, CD81)
Only cancer cells
Dendra2-positive cancer cells
35.0
Dendra2 (green)
b
Cell population (%)
60
40
20
0
Total cancer cells
Dendra2-positive cancer cell
c
Dendra2, H2B (AF 594), DAPI


d
Tumour volume (mm3)
Days
P=0.05
P=0.0001
P<0.0001
Vehicle
L-778123 (80 mg kg−1)
αPD1
αPD1+L-778123 (40 mg kg−1)
αPD1+L-778123 (80 mg kg−1)
αPD1+L-778123 (120 mg kg−1)
e
CD8-positive T cells (%)
P<0.0001
P=0.0002
P=0.0124
P=0.0043
Vehicle
L-778123 (80 mg kg−1)
αPD1
αPD1+L-778123 (40 mg kg−1)
αPD1+L-778123 (80 mg kg−1)
αPD1+ L-778123 (120 mg kg−1)
f
Activated T cells (%)
P=0.0391
Vehicle
L-778123 (80 mg kg−1)
αPD1
αPD1+L-778123 (40 mg kg−1)
αPD1+L-778123 (80 mg kg−1)
αPD1+L-778123 (120 mg kg−1)
g
Cancer cell
T cell
h
Human primary tumour cell
Nanotube
Immune cell
MitoTracker Green, phalloidin red, DAPI
i
Nanotube
Mitochondrial hijacking
Inactivated T cell
Cancer cell
Proposed model for immune evasion

Imunoterapia pra tumores



Imunoterapia pra tumores

Cirurgia
Quimiotarapia
Radioterapia

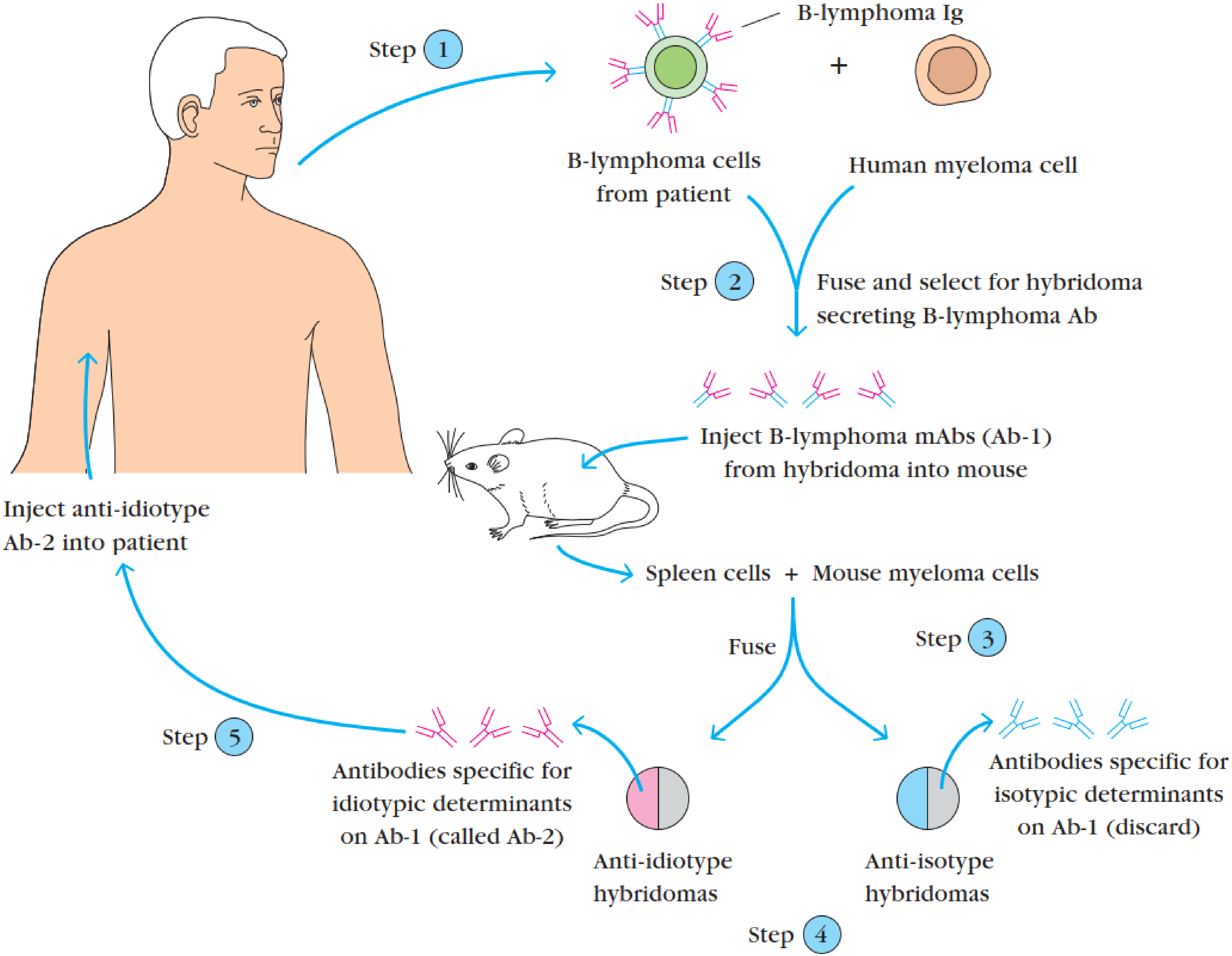
- Náuseas e vômitos severos
- Nefrotoxicidade, hepatoxicidade, cardiotoxicidade, etc...
- Resistência aos medicamentos

E porque não utilizar o próprio sistema imunológico?
Podem ser altamente específicos e não vai lesar a maioria das células.

Anticorpos monoclonais para tratamentos de tumores

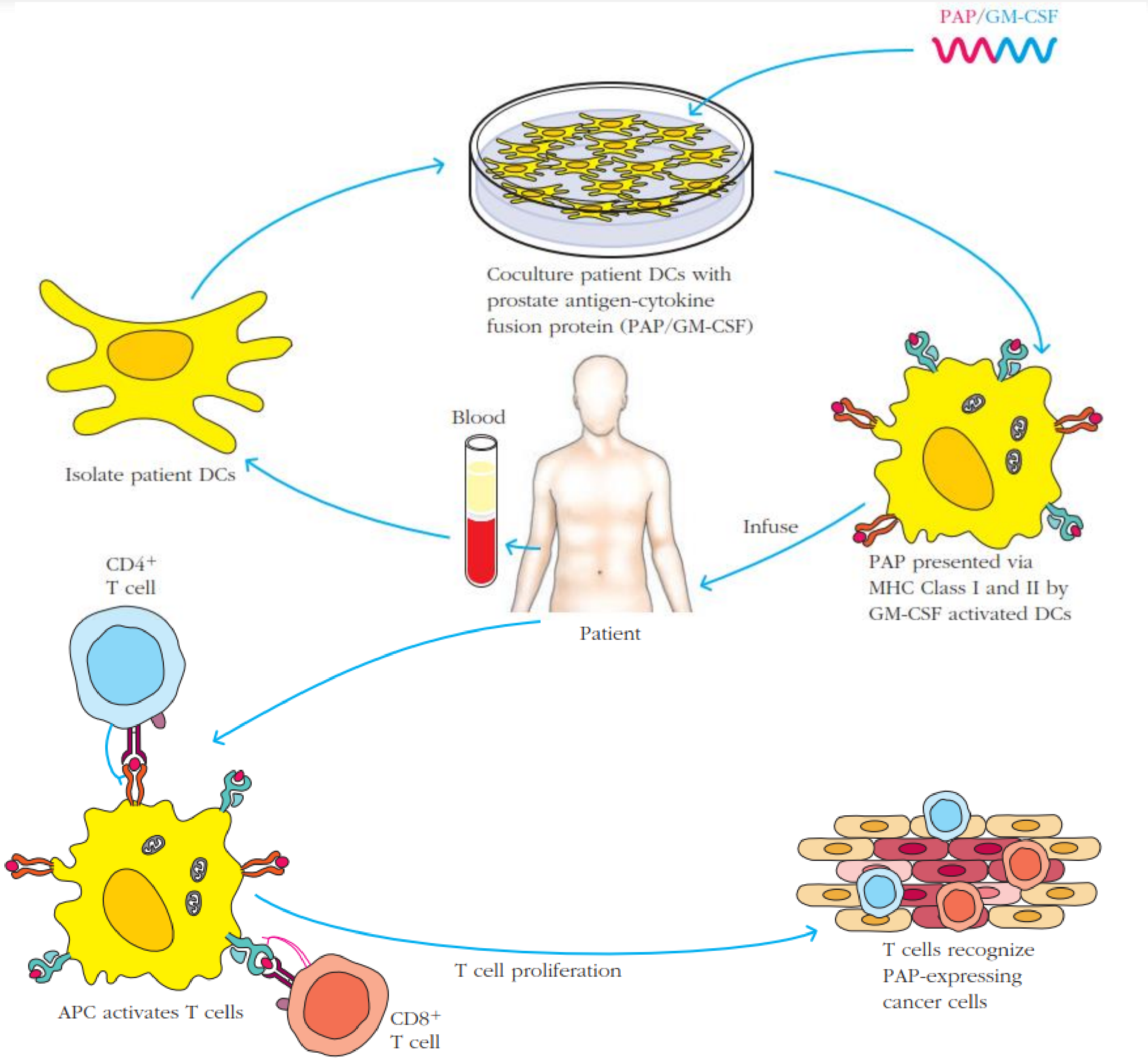
TABLE 19-4 Monoclonal antibodies approved by the FDA and licensed for cancer treatment

mAb name	Trade name	Target	Used to treat	Approved in:
Rituximab	Rituxan	CD20	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia (CLL)	1997 2010
Trastuzumab	Herceptin	HER2	Breast cancer Stomach cancer	1998 2010
Gemtuzumab ozogamicin[2]	Mylotarg	CD33	Acute myelogenous leukemia (AML)	2000[1]
Alemtuzumab	Campath	CD52	CLL	2001
Ibritumomab tiuxetan[2]	Zevalin	CD20	Non-Hodgkin's lymphoma	2002
^{131}I-Tositumomab[2]	Bexxar	CD20	Non-Hodgkin's lymphoma	2003
Cetuximab	Erbitux	EGFR	Colorectal cancer Head and neck cancers	2004 2006
Bevacizumab	Avastin	VEGF	Colorectal cancer Non-small cell lung cancer Breast cancer Glioblastoma and kidney cancer	2004 2006 2008 2009
Panitumumab	Vectibix	EGFR	Colorectal cancer	2006
Ofatumumab	Arzerra	CD20	CLL	2009
Denosumab	Xgeva	Rank ligand	Cancer spread to bone	2010
Ipilimumab	Yervoy	CTLA-4	Melanoma	2011
Brentuximab vedotin[2]	Adcetris	CD30	Hodgkin's lymphoma and one type of non-Hodgkin's lymphoma	2011


Step 1
B-lymphoma Ig
+
B-lymphoma cells from patient
Human myeloma cell
Step 2
Fuse and select for hybridoma secreting B-lymphoma Ab
Inject B-lymphoma mAbs (Ab-1) from hybridoma into mouse
Inject anti-idiotype Ab-2 into patient
Spleen cells + Mouse myeloma cells
Fuse
Step 3
Step 5
Antibodies specific for idiotypic determinants on Ab-1 (called Ab-2)
Anti-idiotype hybridomas
Anti-isotype hybridomas
Antibodies specific for isotypic determinants on Ab-1 (discard)
Step 4

Vacinas para tratamentos de tumores

- Células tumorais mortas
- Antígenos recombinantes
- Células dendríticas



Sobrevida de 4 meses
93 mil dólares

Terapia de células T com receptor antigênicos quimérico

Terapia adotiva
Usa células T com expressão de receptores antigênicos quiméricos – CAR

1) Células T isoladas do paciente
2) Expandidas
3) Transfectadas com vetores virais codificadores de CAR
4) Inoculadas de volta no paciente

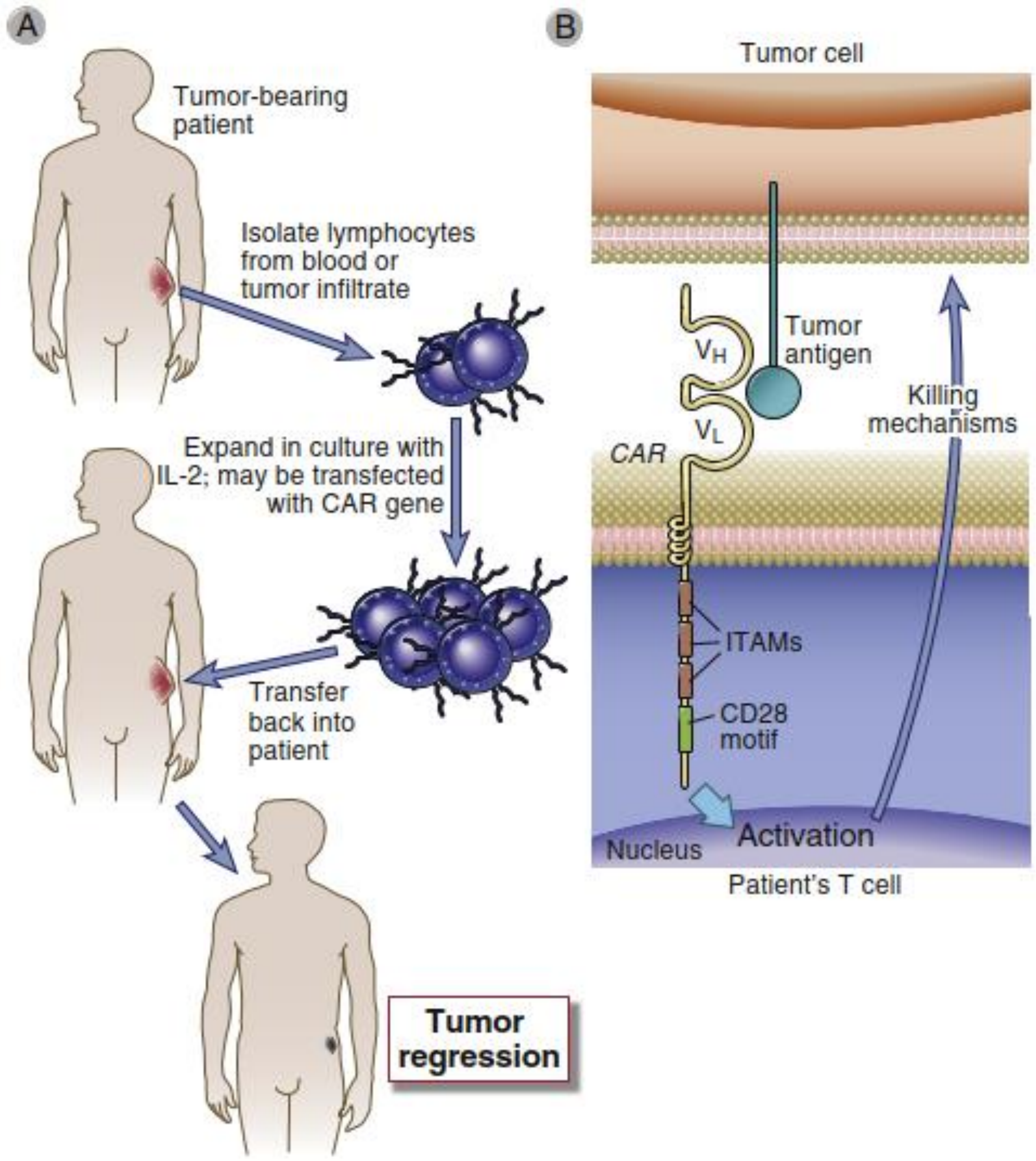


FIGURE 18-6 Adoptive cellular therapy. Lymphocytes isolated from the blood or tumor infiltrate of a patient may be expanded by culture in IL-2 and infused back into the patient **(A)**. The lymphocytes may be transfected with CAR genes **(B)**. This treatment, often combined with systemic IL-2 administration, leads to tumor regression in some patients. In some cases, the patient's T cells may be genetically transduced ex vivo to express recombinant chimeric antigen receptors (CARs) before transfer back into the patient. CARs **(B)** are composed of receptor domains specific for tumor antigens, and signaling domains, such as ITAMs and cytosolic motifs of CD28, which promote robust T cell activation.

Abbas 8ª ediçao

Será que teremos uma cura para o câncer?

Obrigada pela atenção!