Focus on Immunotherapy as a Targeted Therapy

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BC Cancer, Victoria, Canada
FPON, Oct 18 2018

Disclosures

- I have nothing to disclose that is relevant to this presentation.

Immunology @ Deeley Research Centre

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

Current treatments for cancer

Surgery

Radiation therapy

Chemotherapy

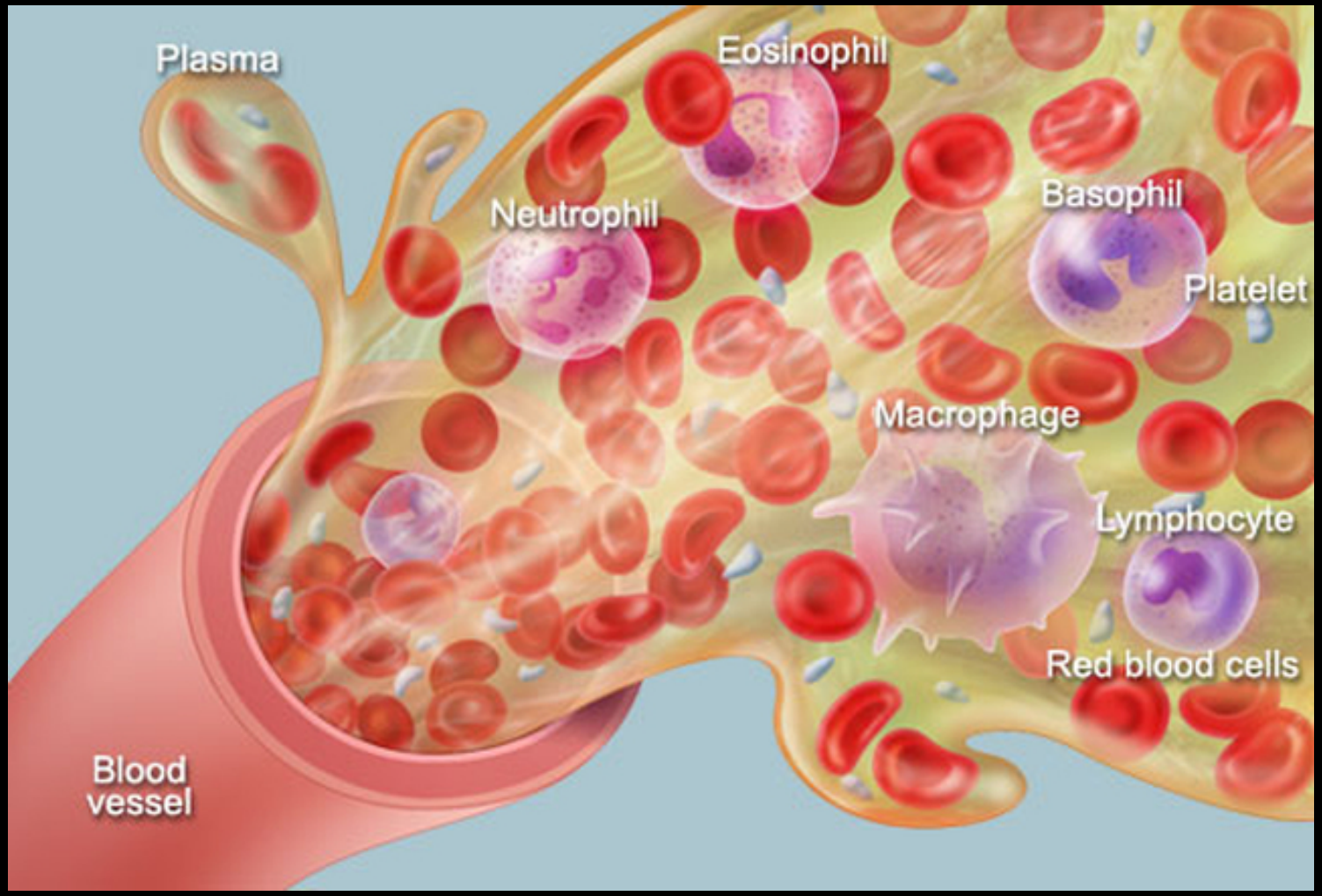
Hormonal therapy

Targeted therapies (antibodies, small molecules)

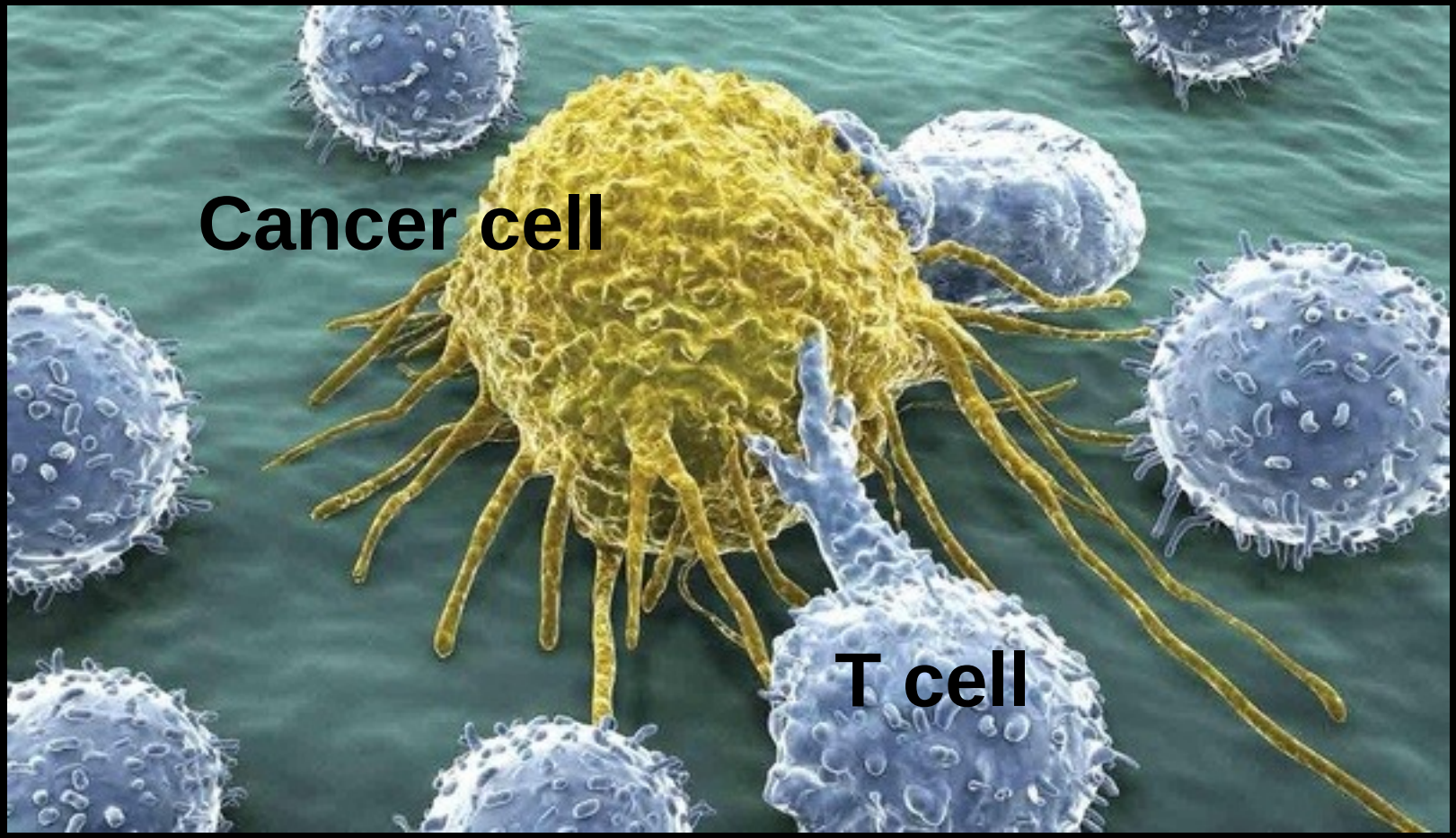
New!

Immunotherapy

The immune system



T cells can recognize and destroy cancer cells



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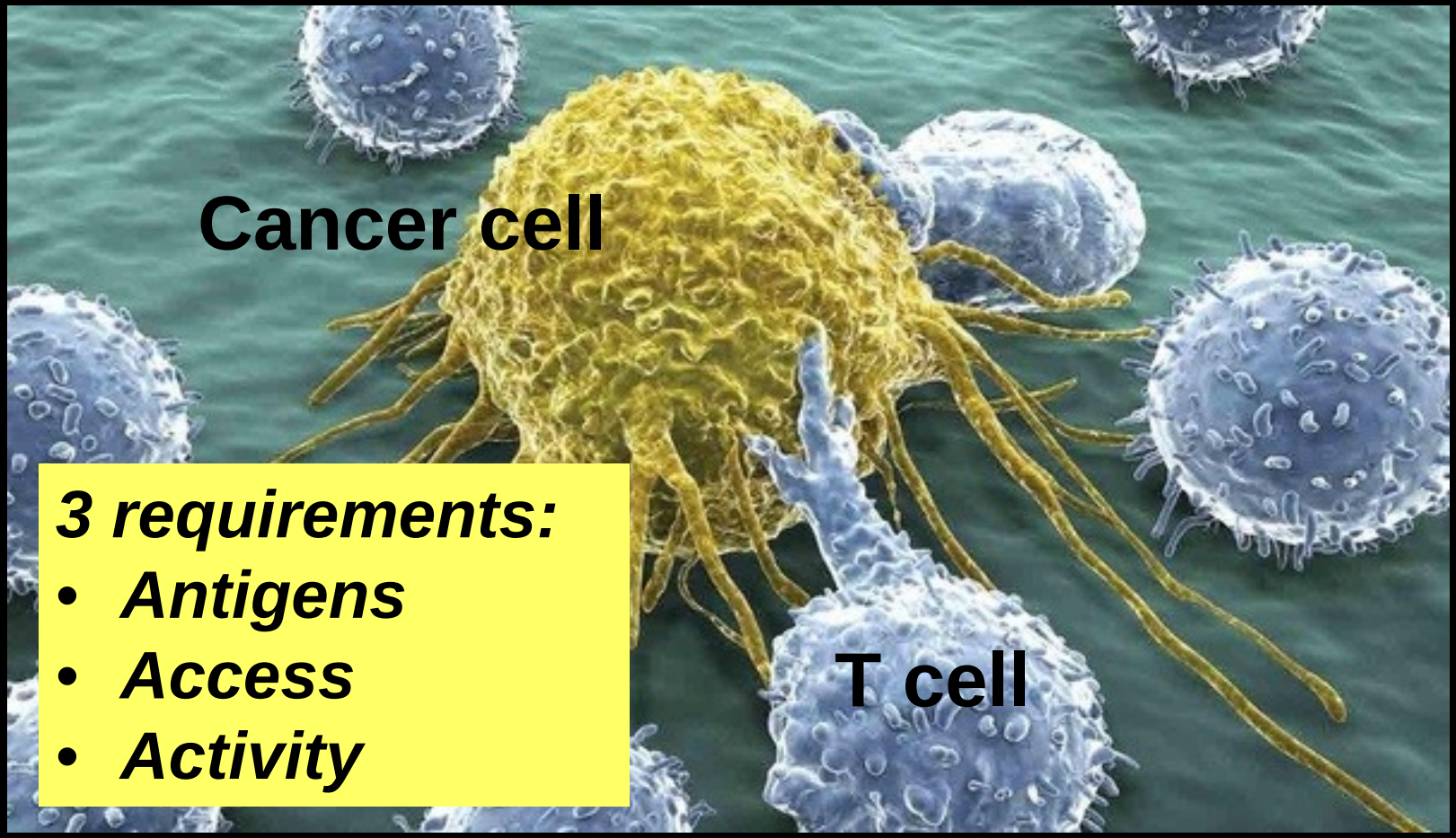


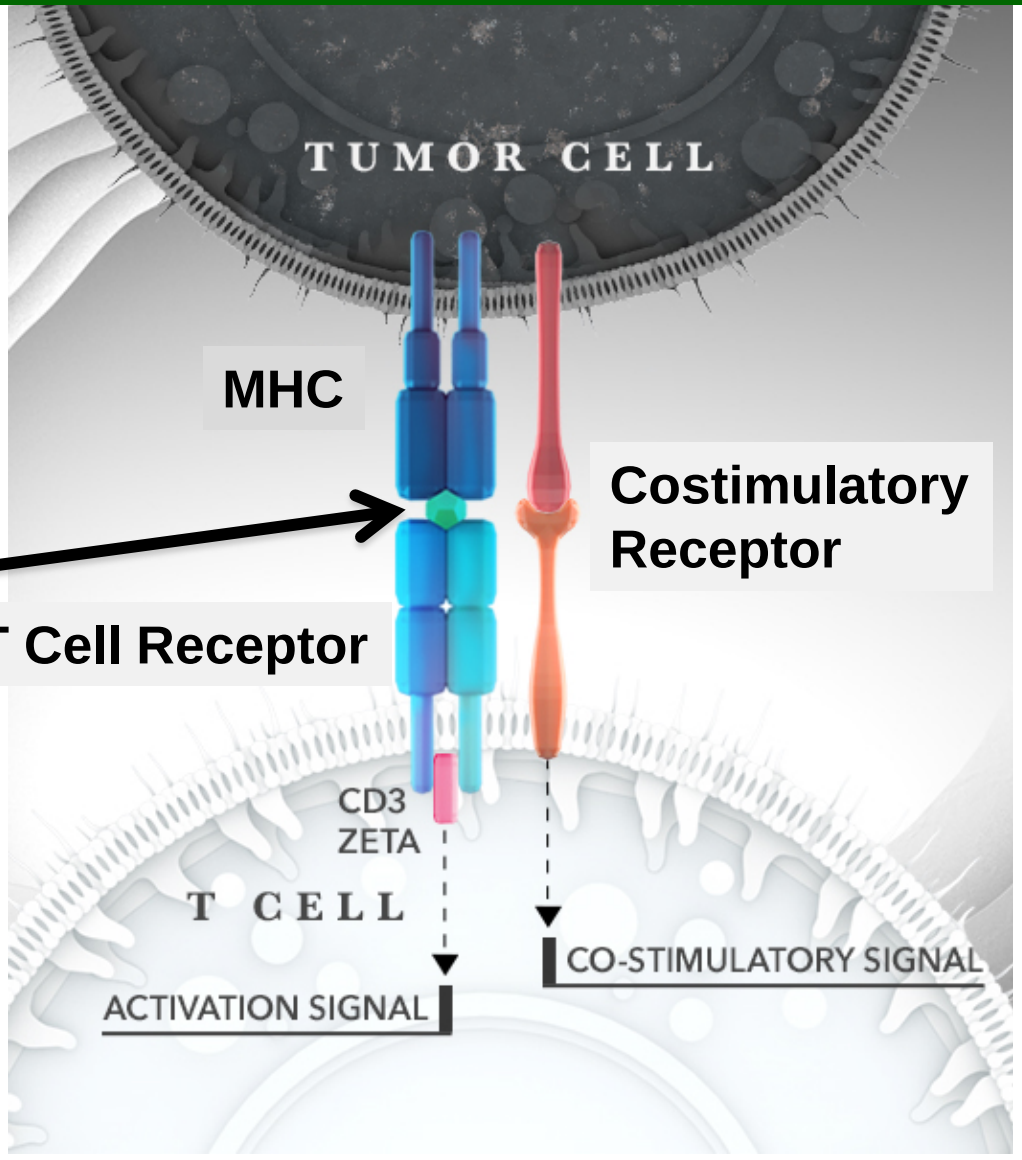
3 requirements:

- ***Antigens***
- ***Access***
- ***Activity***

Recognition of tumor cells by T cells

Antigen (epitope)

- self protein → tolerance
- mutated protein (neoantigen)
- cancer-testis (CT) antigen
- oncofetal protein
- overexpressed protein
- endogenous retroviral ORFs
- viral protein (e.g. HPV, EBV)



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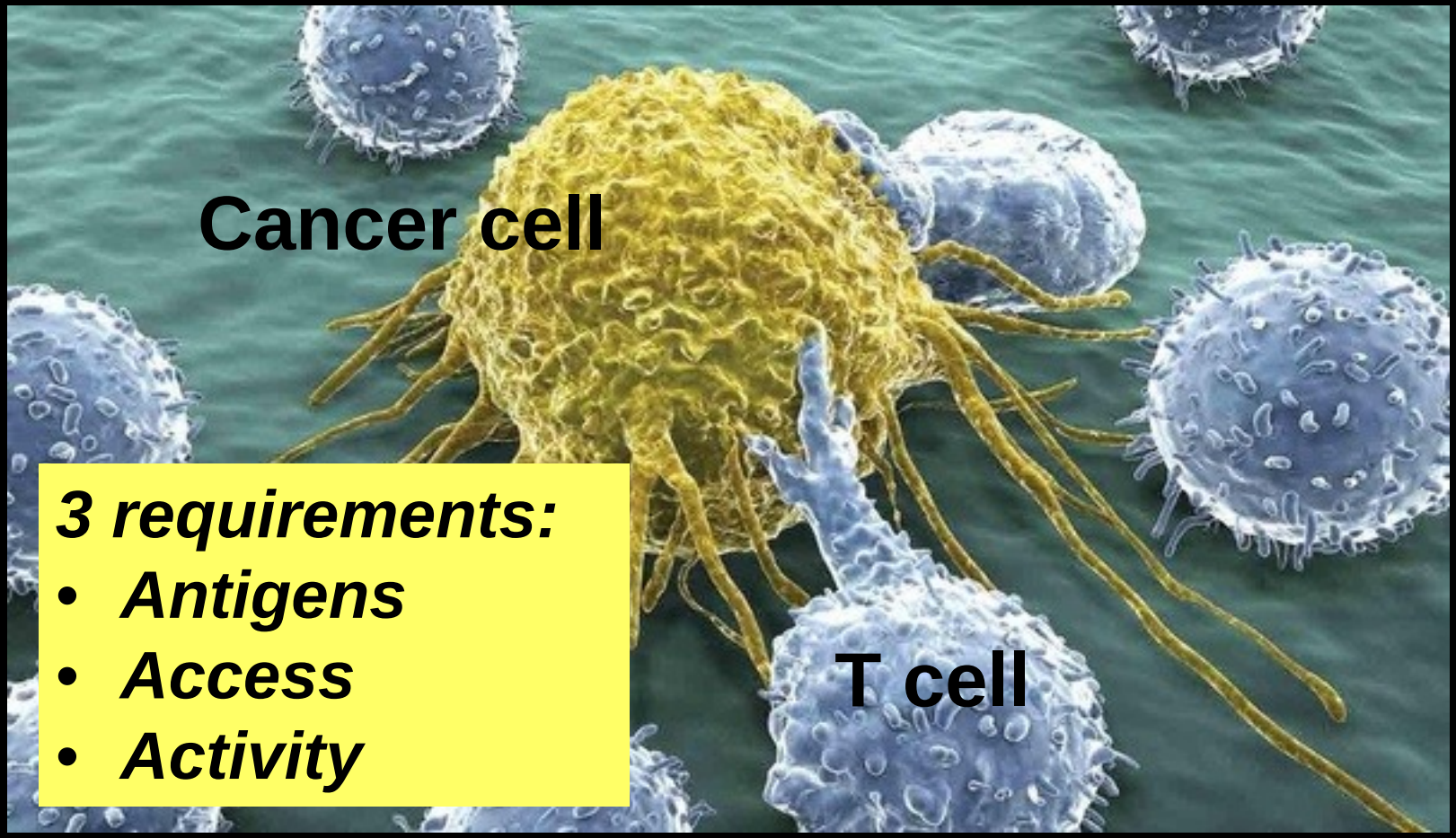

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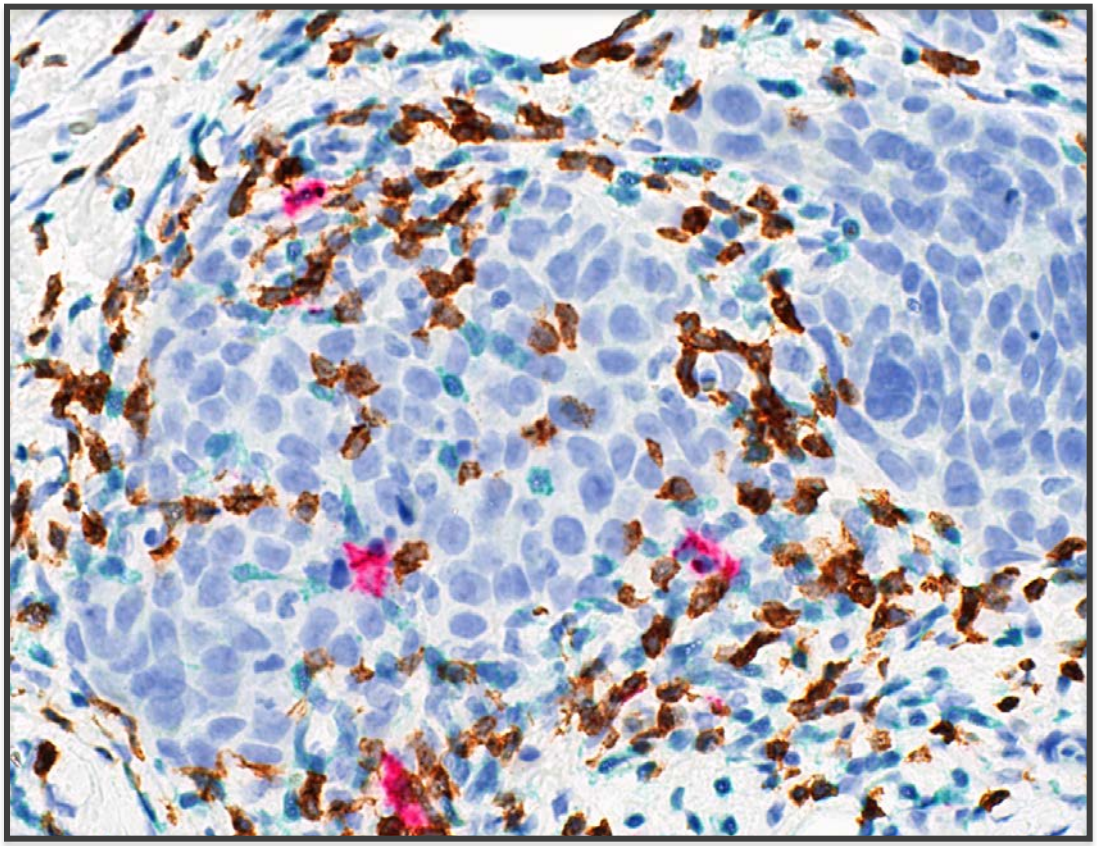
Tumor-infiltrating lymphocytes (TIL) in ovarian cancer

Multi-colour IHC with Nuance imaging



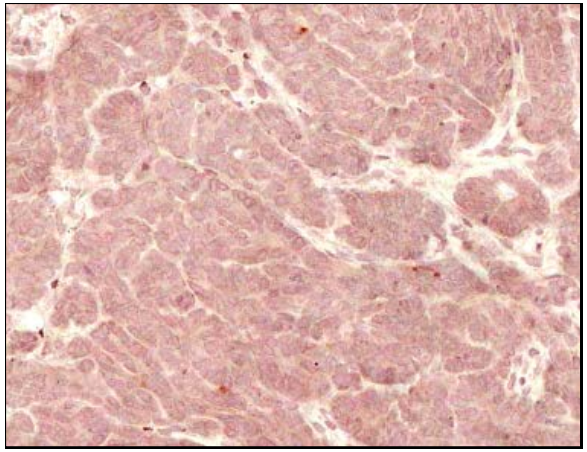
CD8+ killer T cells
CD4+ T cells
CD20+ B cells
Tumor cells

Katy Milne, unpublished

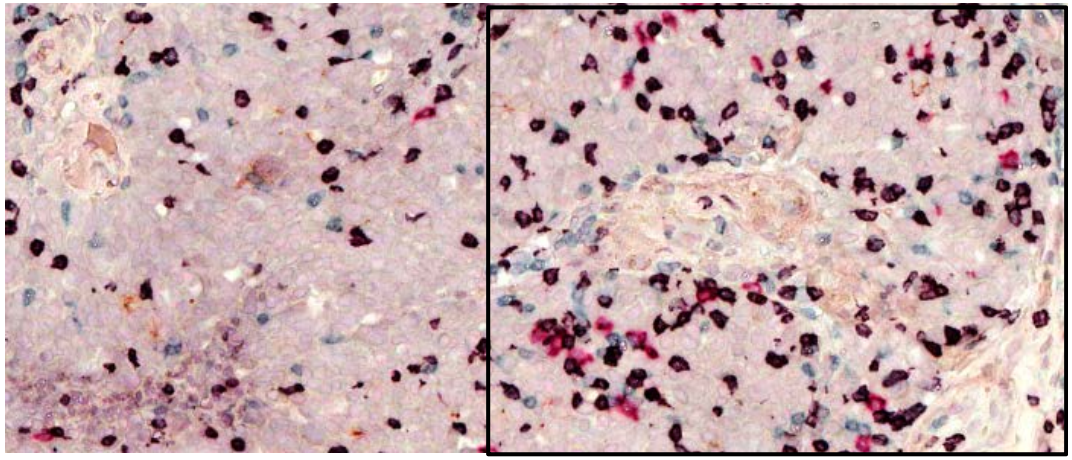
Tumor-infiltrating lymphocytes (TIL) in ovarian cancer

CD4+ T cells
CD8+ T cells
CD20+ B cells

Three cases of HGSC:



Cold
Few TIL

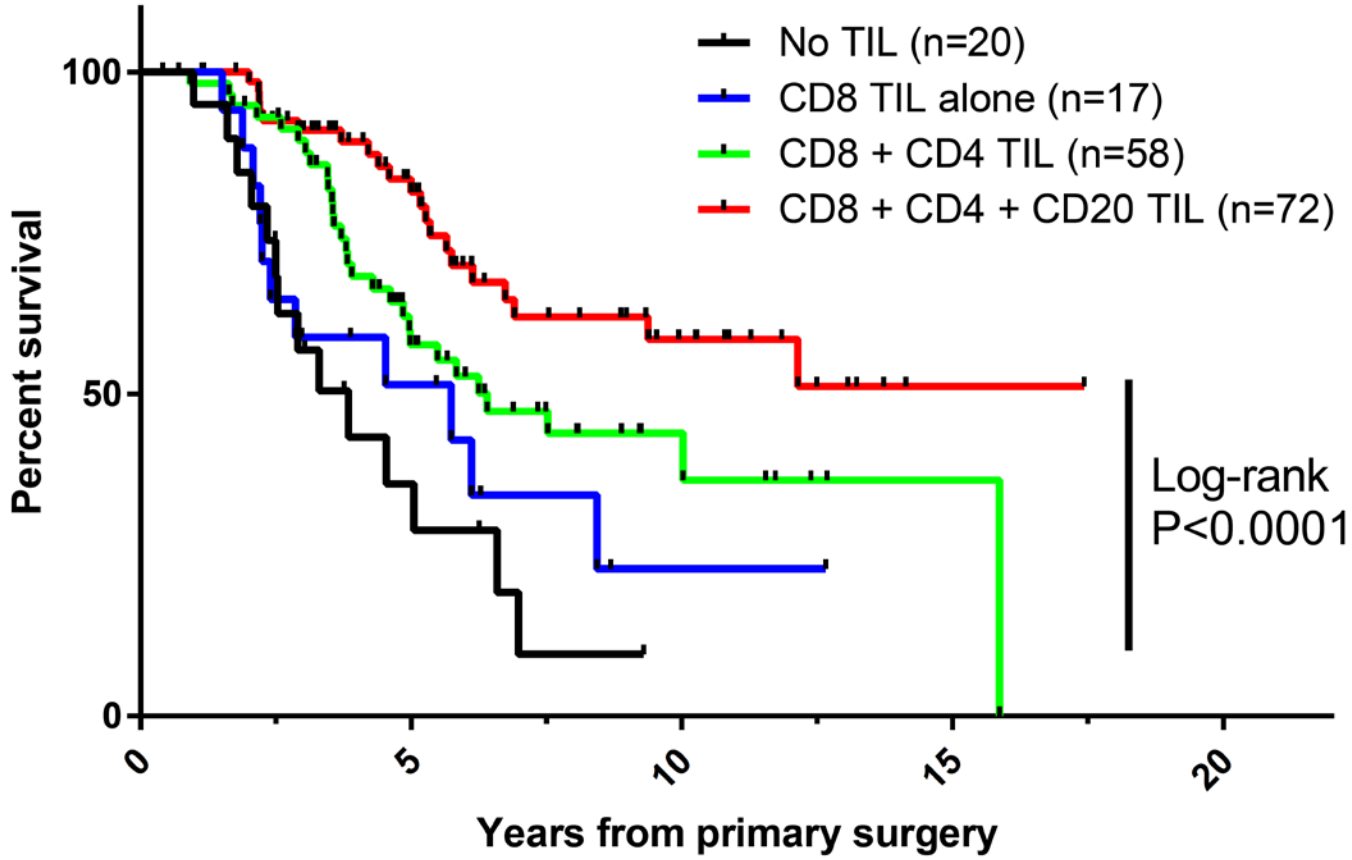


Warm
Weak TIL
T cells in stroma

Hot
Robust TIL
T cells and B cells in epithelium & stroma

T cells and B cells show a combined effect on survival

Kaplan-Meier based on TIL patterns in HGSC (n=167, optimally de-bulked)

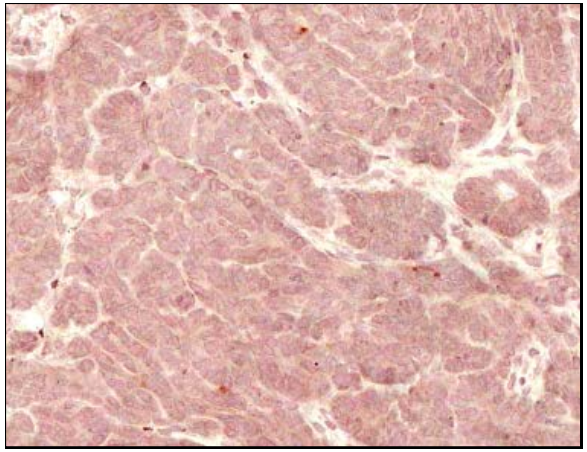


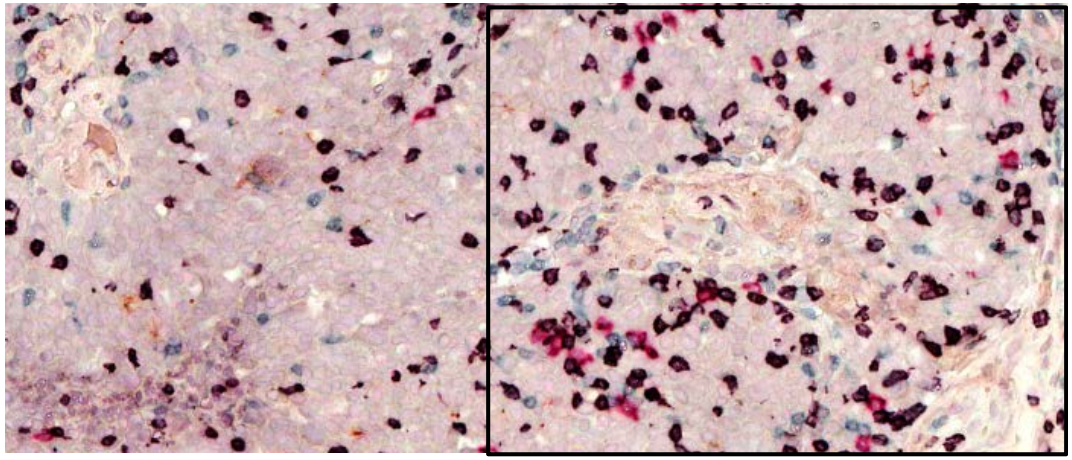
Julie Nielsen et al, Clin Can Res 2012

Why aren’t hot tumors rejected?

Three cases of HGSC:

CD4+ T cells
CD8+ T cells
CD20+ B cells





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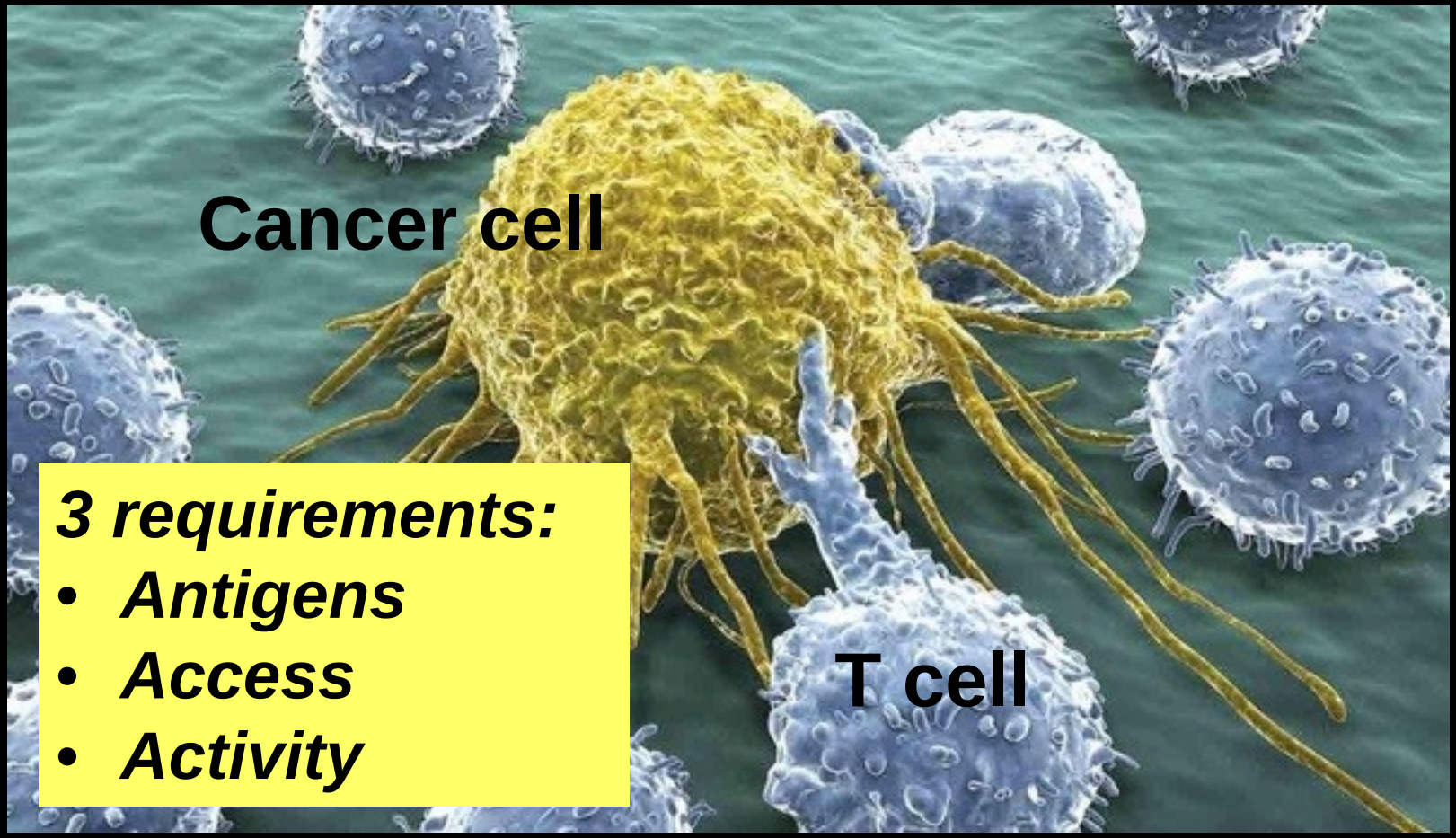

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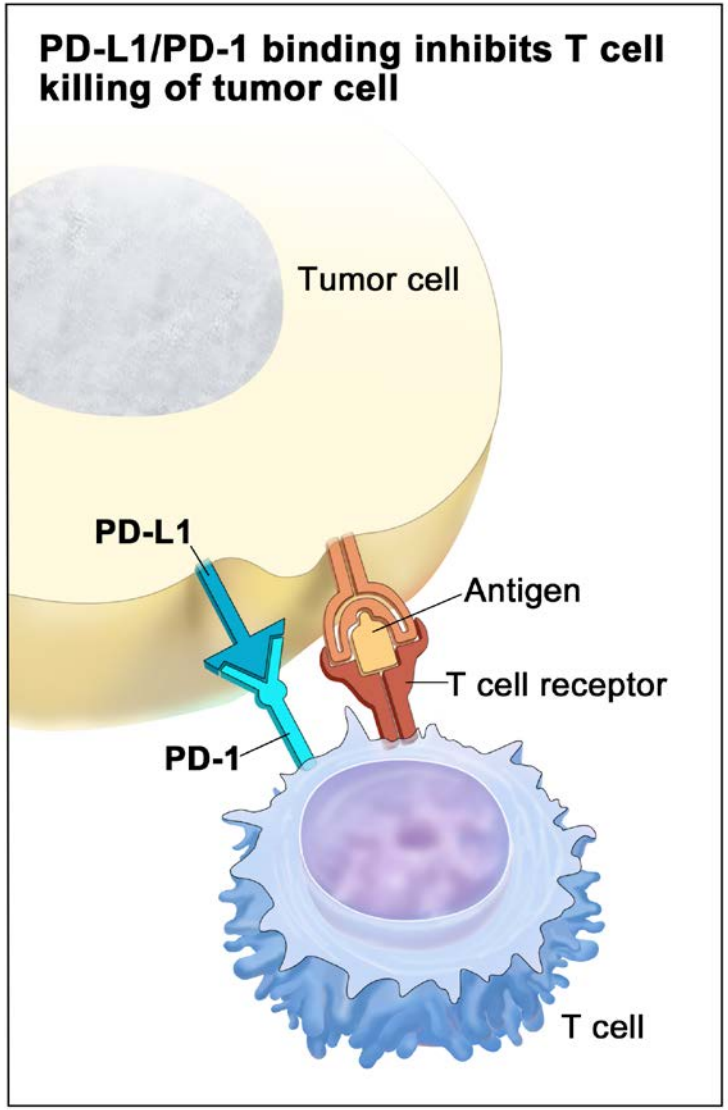
Immune evasion mechanisms: Inhibitory signals (immune checkpoints)



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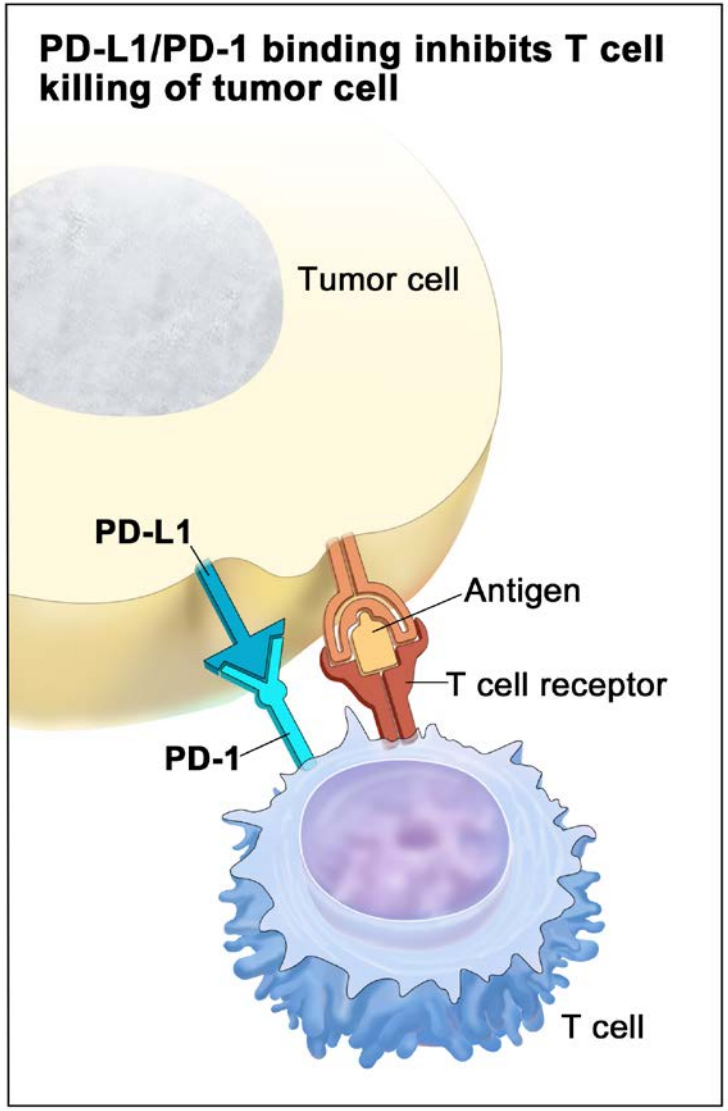

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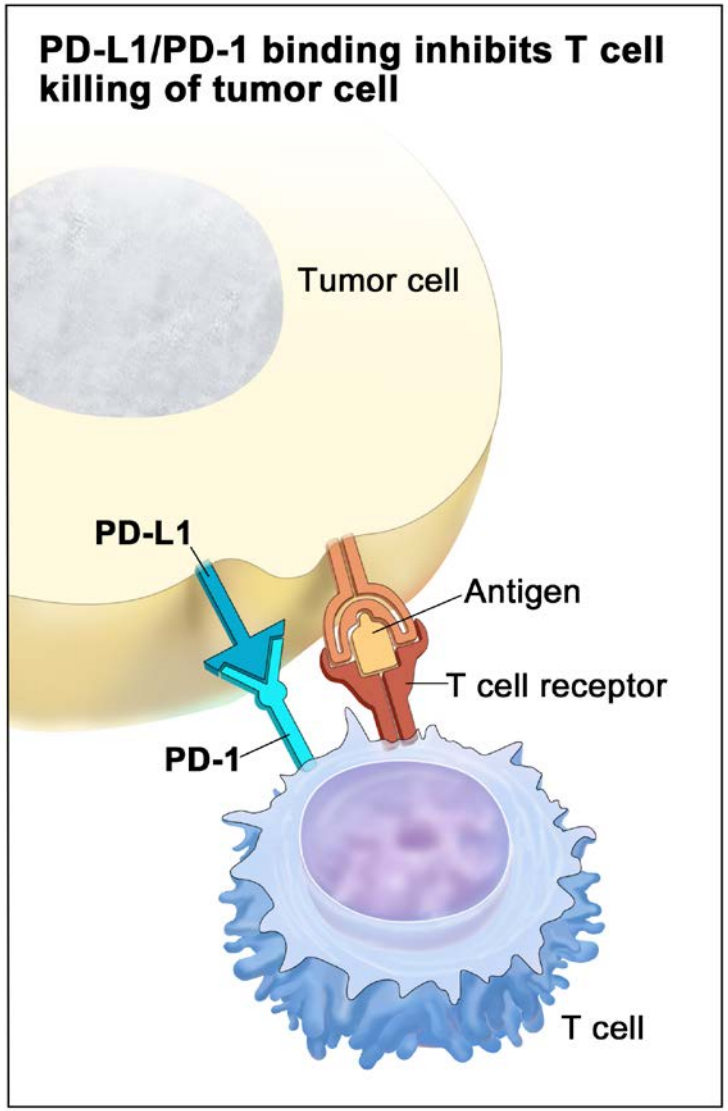

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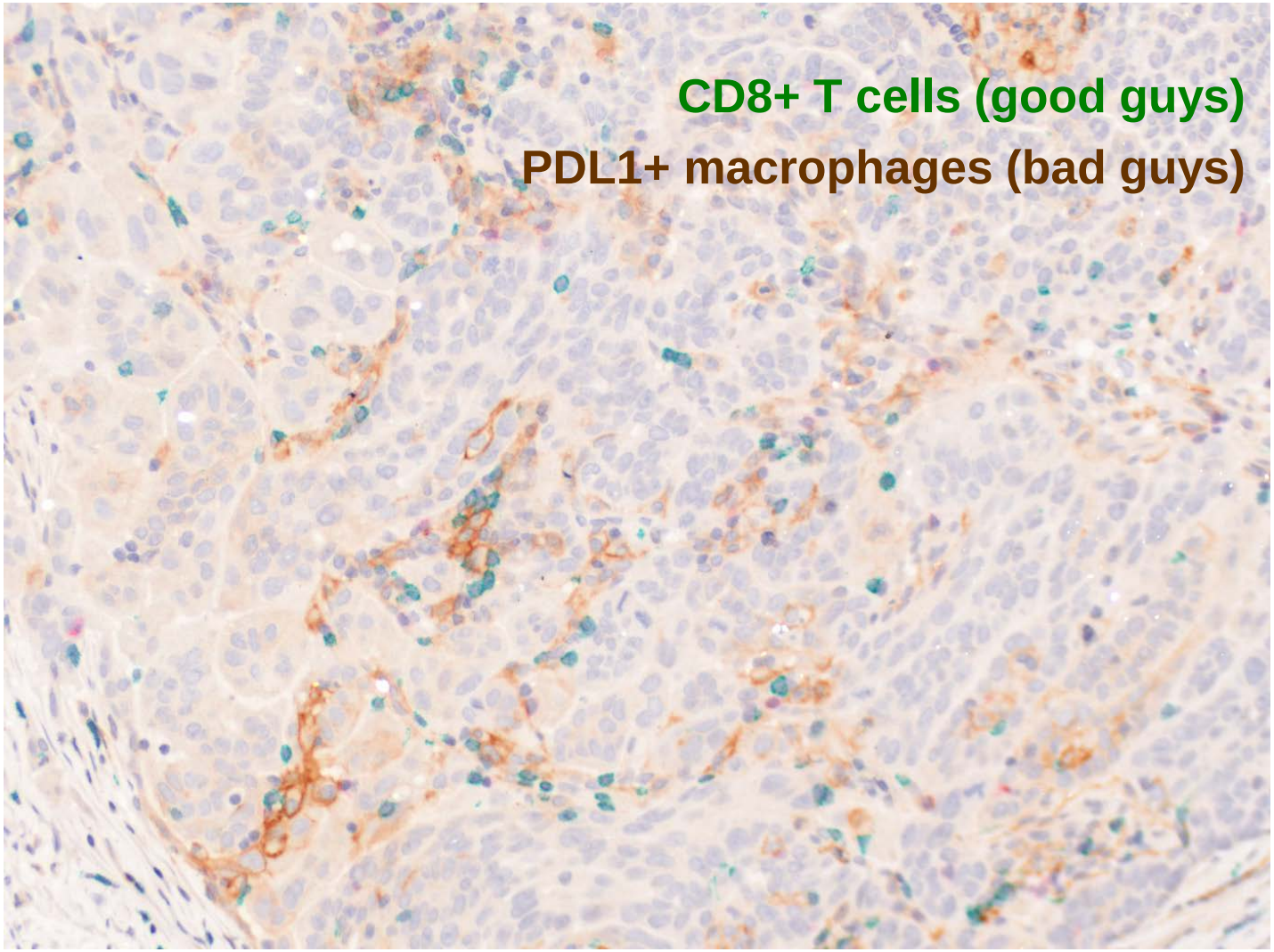
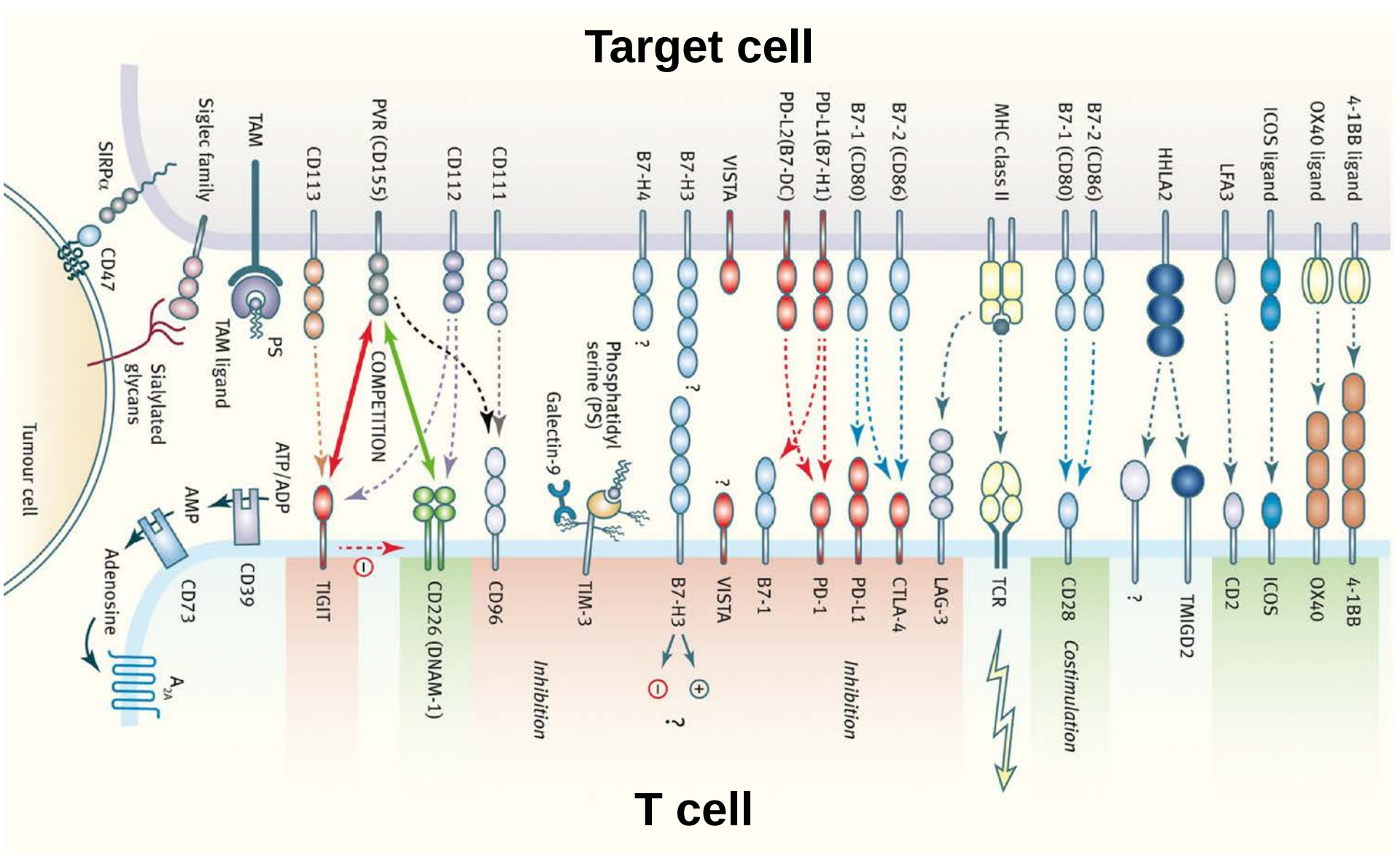


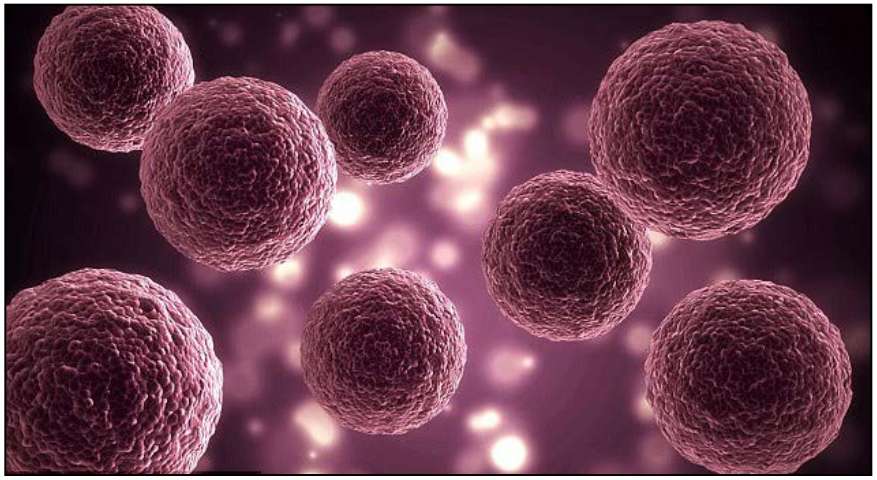
Immune evasion mechanisms: Inhibitory signals (immune checkpoints)

Stimulatory and inhibitory pathways in T cells



T cells have very sophisticated control mechanisms

Immunotherapy modalities

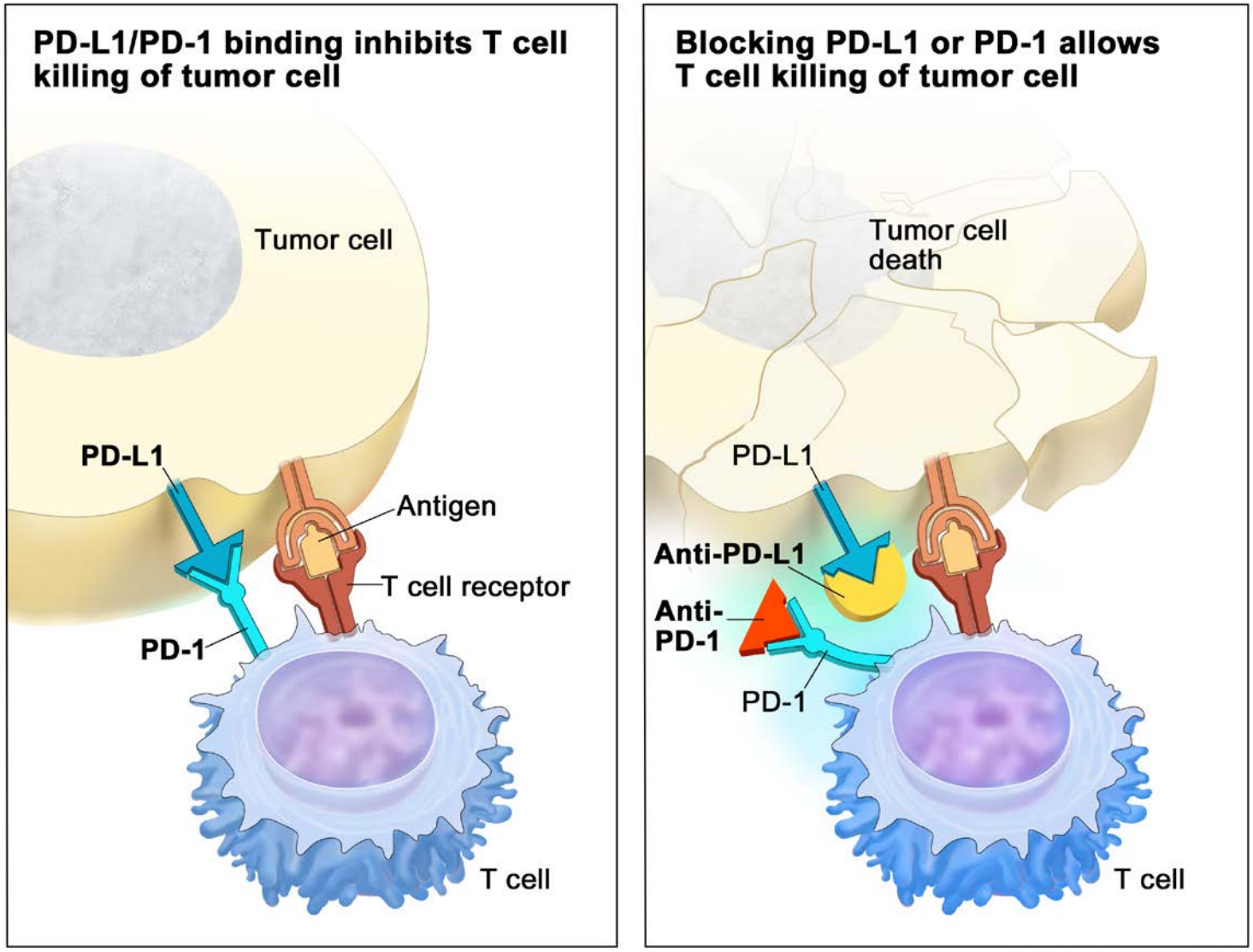


Antibodies (e.g. anti-PD-1)
Other immune modulators
Vaccines
Oncolytic viruses

Adoptive T cell therapy

- **Natural (e.g. TIL)**
- **Engineered (e.g. CAR-T cells)**

Immune modulation: Checkpoint blockade



Checkpoint blockade: clinical successes

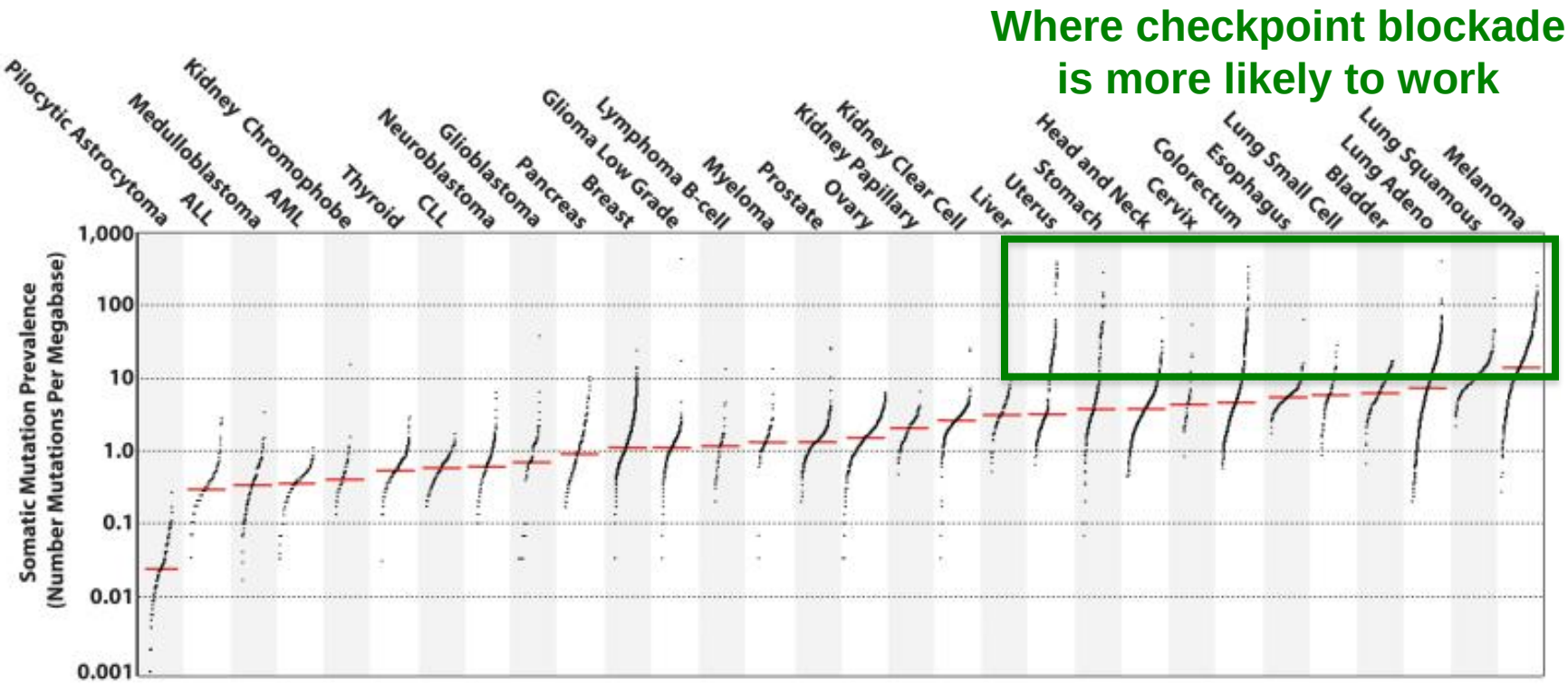
anti-CTLA-4 (eg, Ipilimumab)

- Metastatic melanoma – **FDA approval**

anti-PD-1 (eg, Nivolumab, Pembrolizumab, others):

- Metastatic melanoma – 38% Objective Responses (Hamid, NEJM 2013), 53% Objective Responses with Ipilimumab (Wolchok, NEJM 2013) and **FDA approval**
- Non-small cell lung cancer – 18% Objective Responses and **FDA approval**
- Kidney cancer – 27% Objective Responses (Topalian, NEJM 2012); 52% ORR nivolumab + sunitinib (Amin, JCO abstract, 2014), **FDA approval**
- Bladder cancer – 52% Objective Responses (Powles, Nature 2014), **FDA approval**
- Hodgkin's Lymphoma – 87% Objective Responses (Ansell, NEJM 2015), **FDA approval**
- Colorectal cancer (MSI) – 40% Objective Responses (Le, NEJM 2015), **FDA Breakthrough Status 2015**
- Any adult or pediatric metastatic solid tumor with mismatch repair deficiency (dMMR), **FDA approval**
- **Replacing frontline chemotherapy** for melanoma, lung cancer and renal cell cancer (so far)

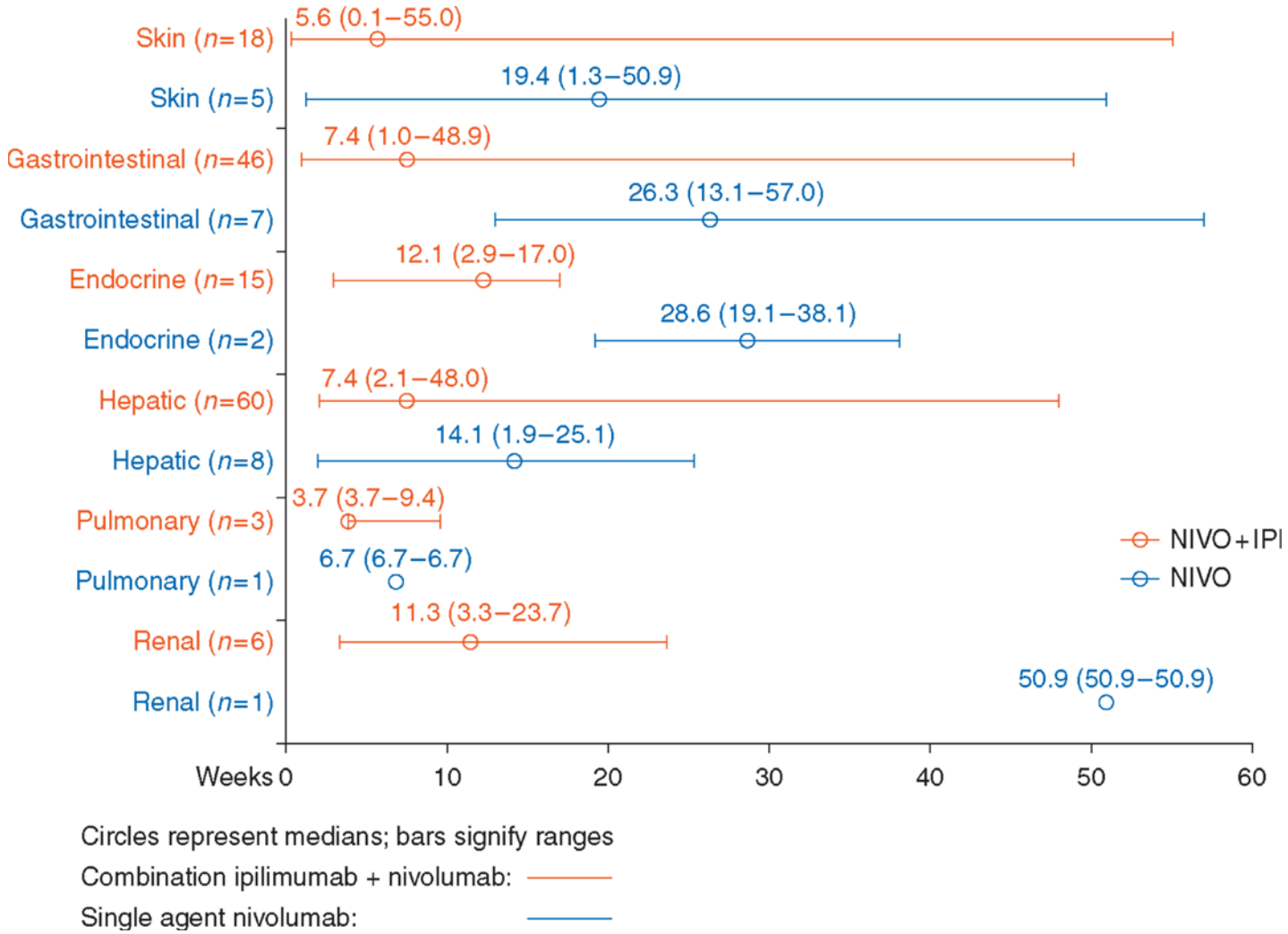
Mutation load predicts response to checkpoint blockade (imperfectly)



Immune modulation: current challenges

Toxicities

Haanen et al. ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4). PubMed PMID: 28881921.



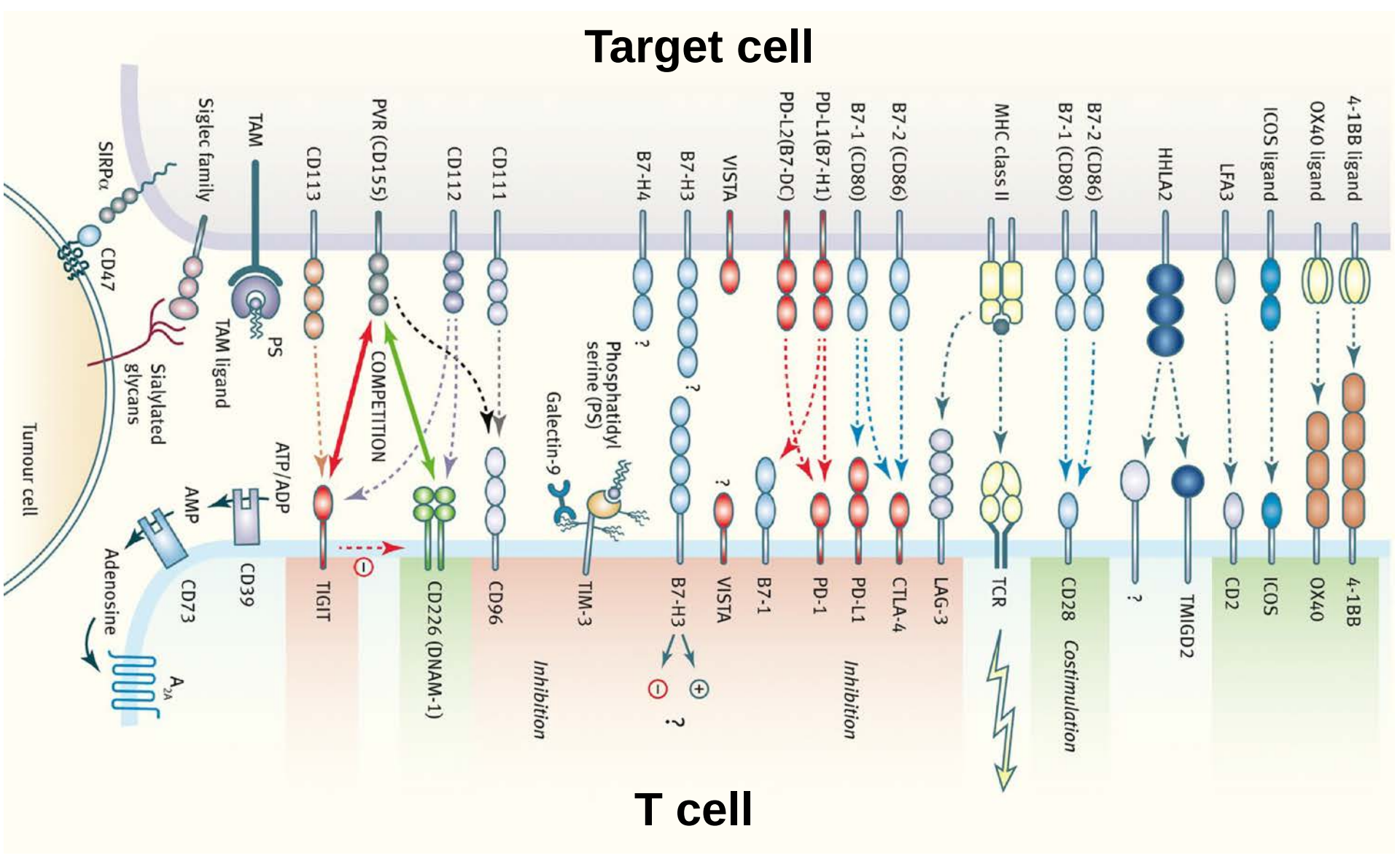
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
Ann Oncol. 2017;28(suppl_4):iv119-iv142. doi:10.1093/annonc/mdx225

Immune modulation: current challenges

Efficacy

- many cancers (e.g., ovarian, breast) have low response rates (10-20% range)
- responses are often transient (e.g., lung)

Stimulatory and inhibitory pathways in T cells

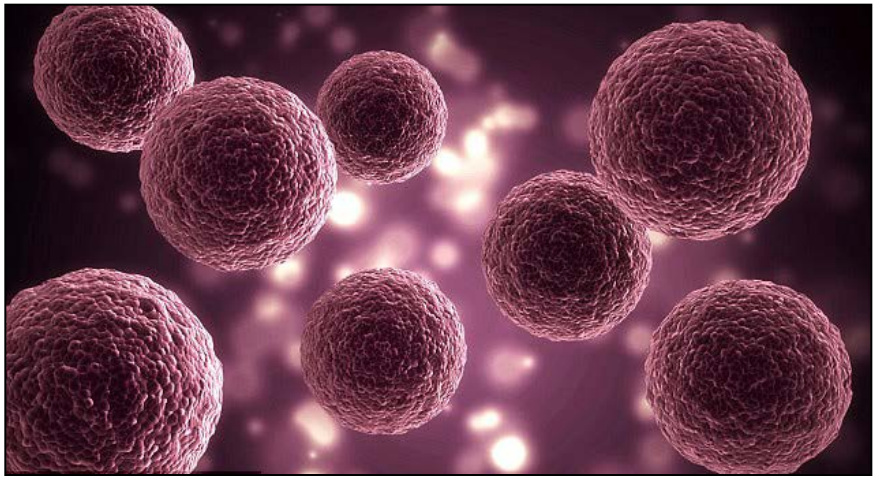


Immune modulation: current challenges

Cost

- approx. $100k/treatment cycle
- combinations may be required for some cancers (e.g., Ipi + Nivo for melanoma)
- long-term use may be required for some cancers

Immunotherapy modalities



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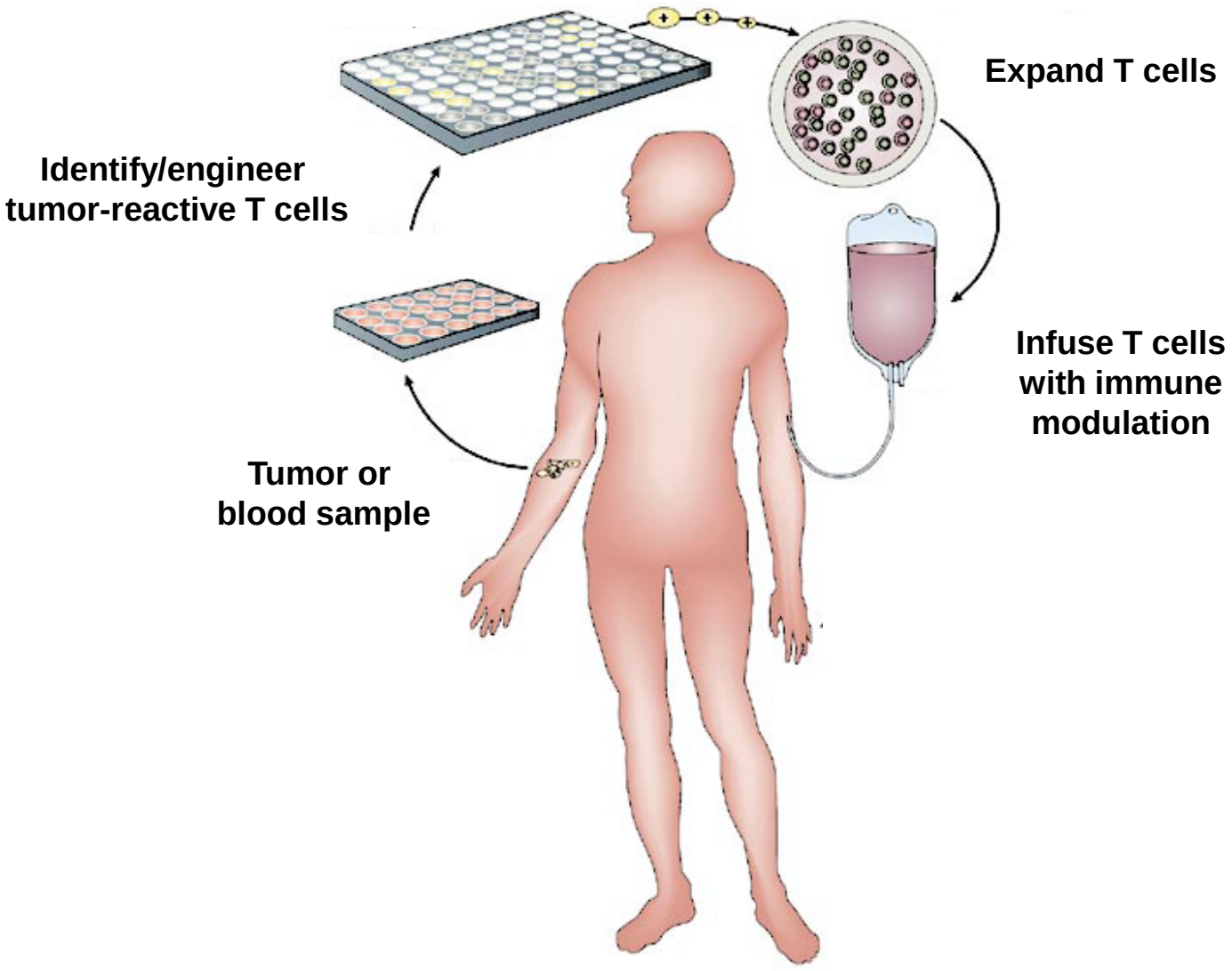
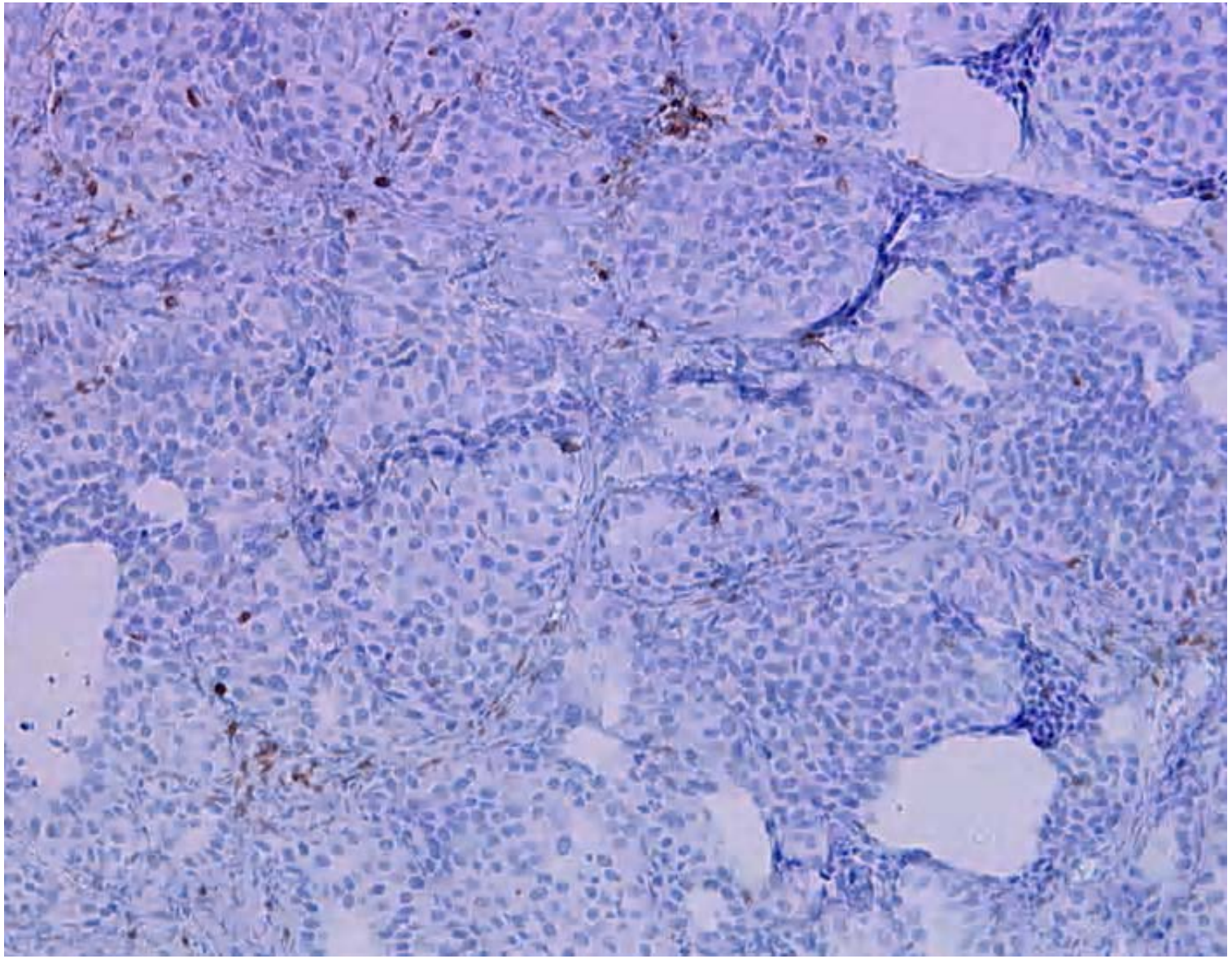
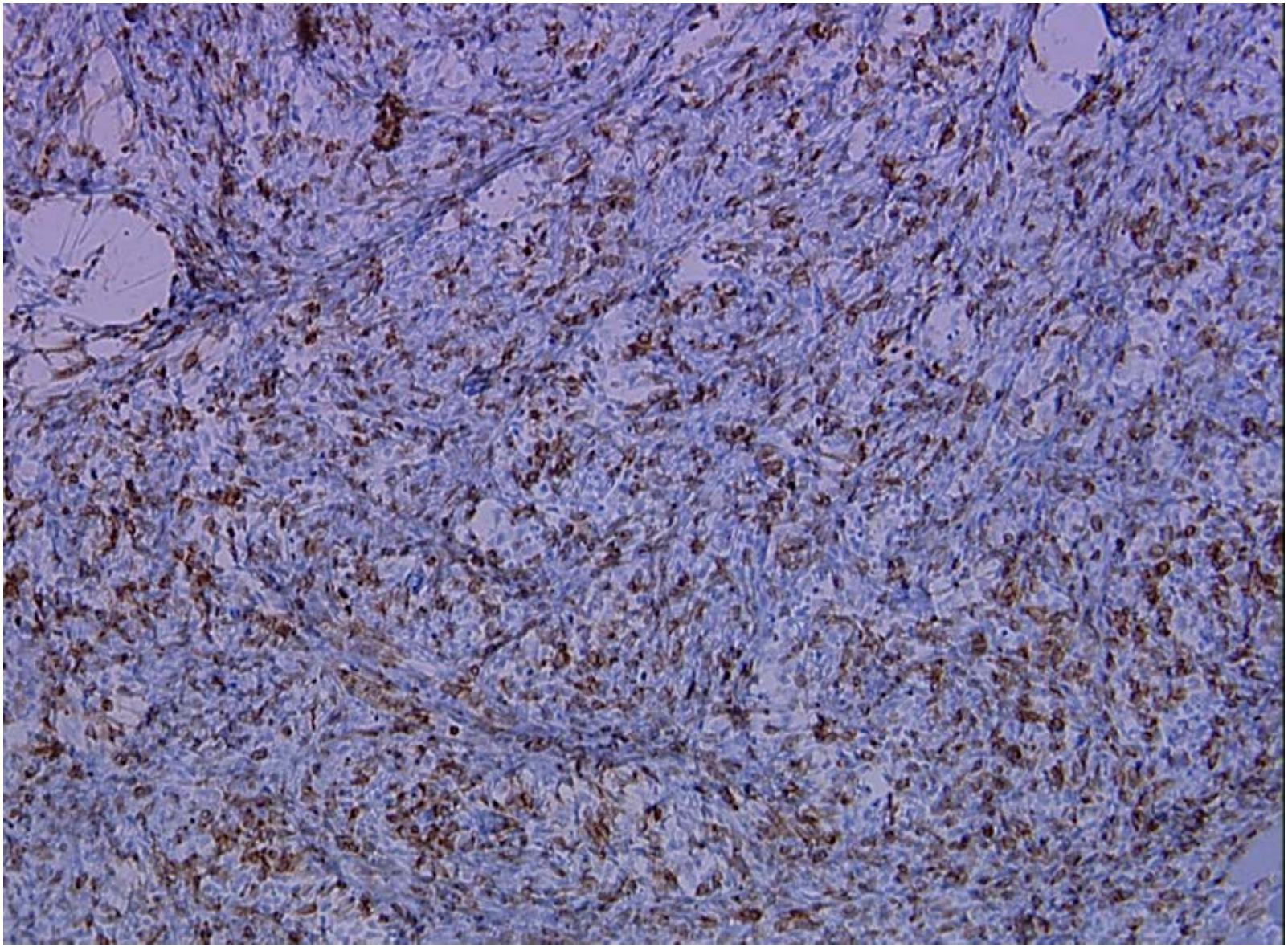


Mouse breast tumour before T cell therapy



anti-CD3 (T cell marker)

Mouse breast tumour 5 days after T cell therapy



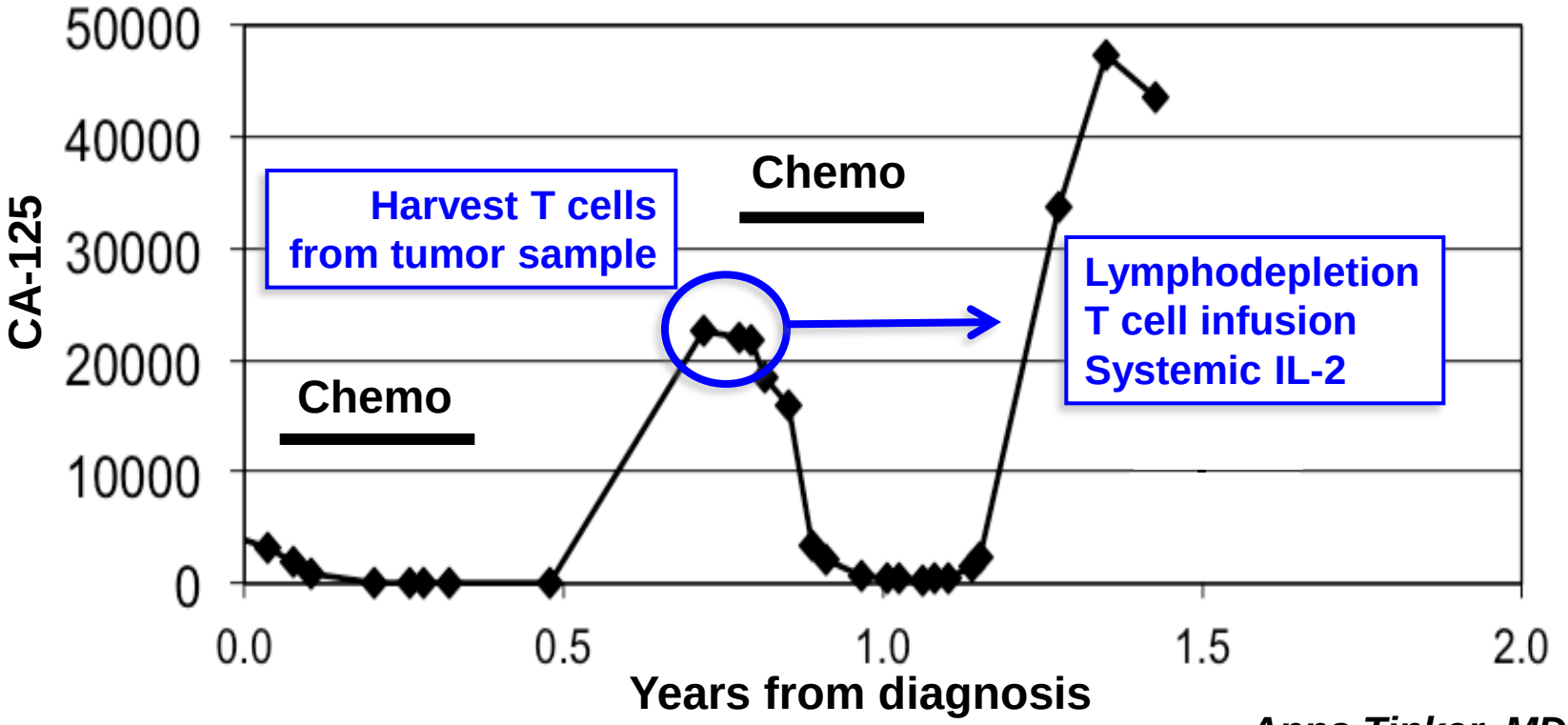
anti-CD3 (T cell marker)

Clinical grade T cell production unit

BCCA's Deeley Research Centre, Victoria

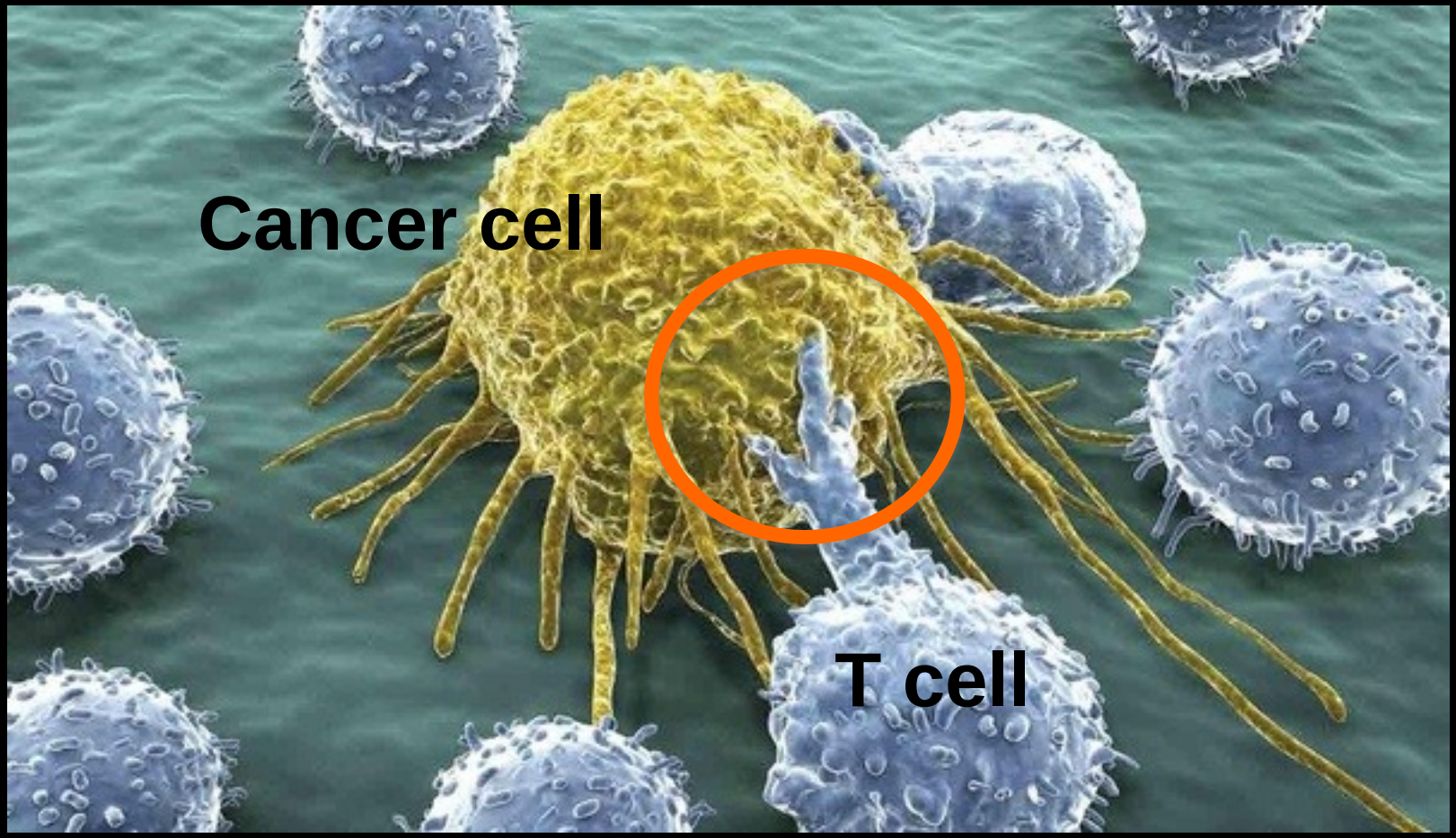
BC Cancer Gyne TIL Trial (2019)

Relapsed cervical and MMR deficient ovarian and endometrial cancers

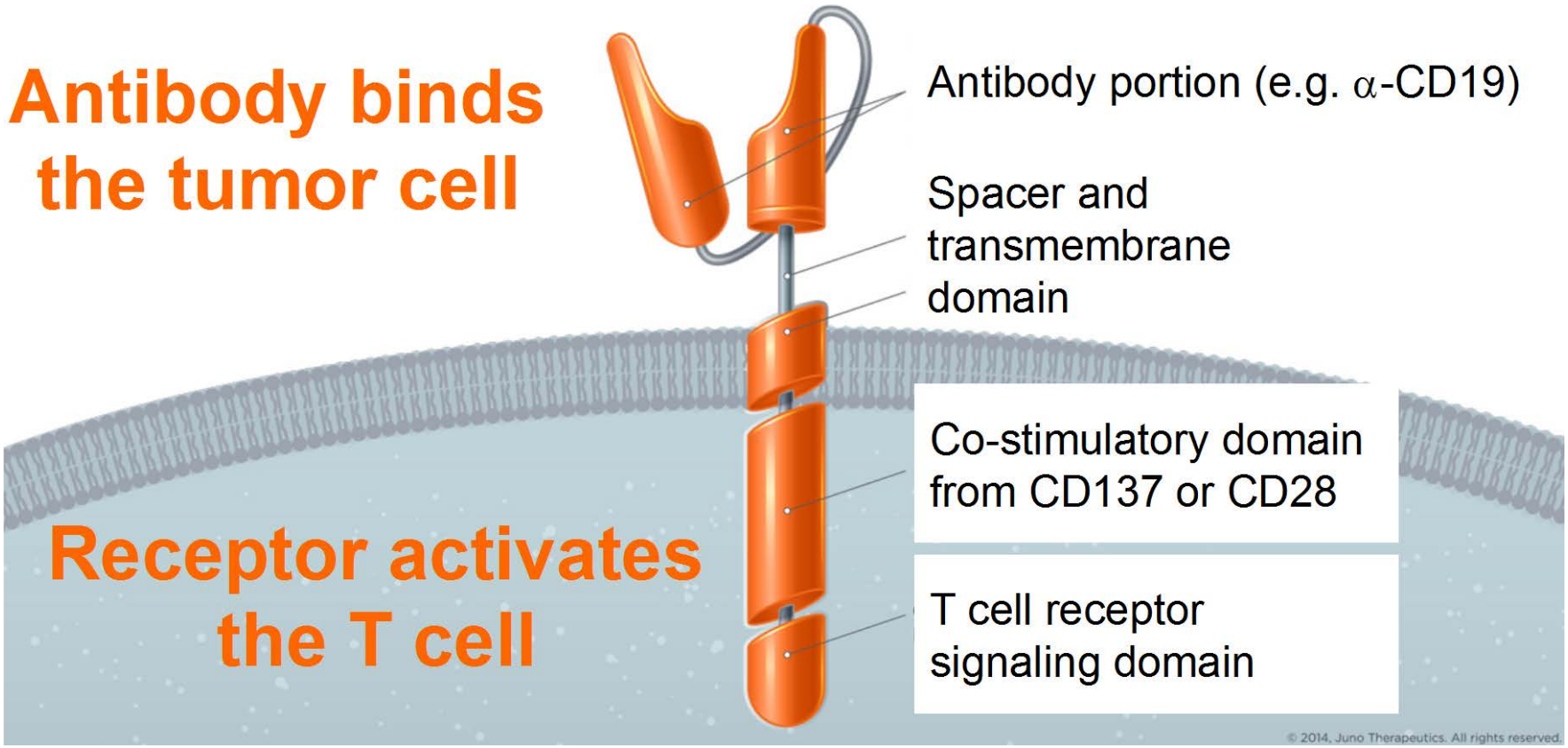


Anna Tinker, MD
Raewyn Broady, MD
Brad Nelson, PhD
John Webb, PhD
Rob Holt, PhD

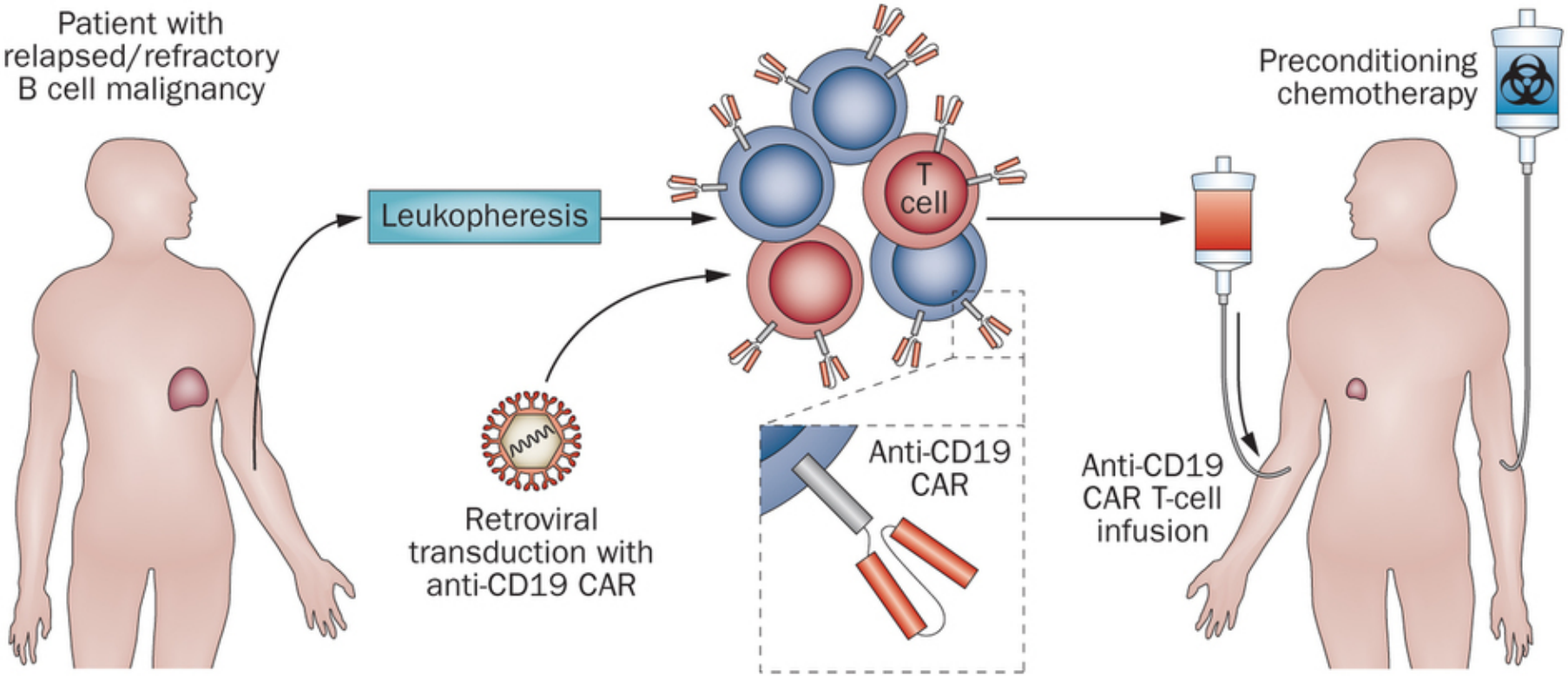
Engineering T cells to better recognize and destroy cancer cells



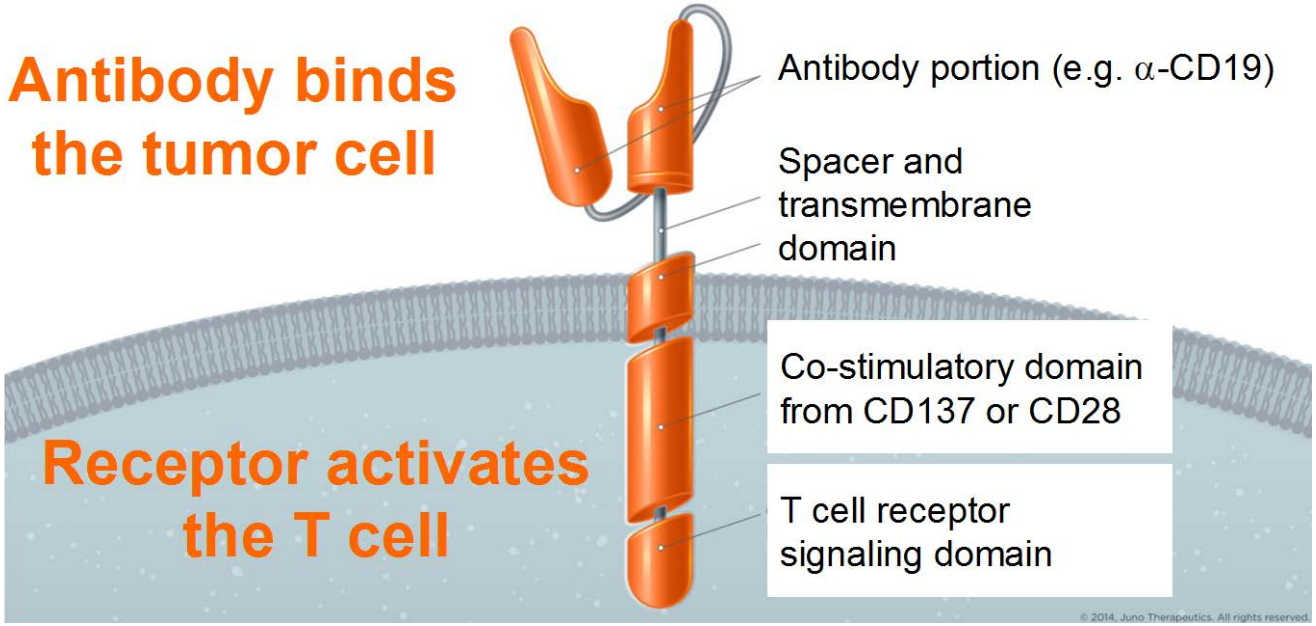
Chimeric Antigen Receptors (CARs)



CAR-T cell therapy

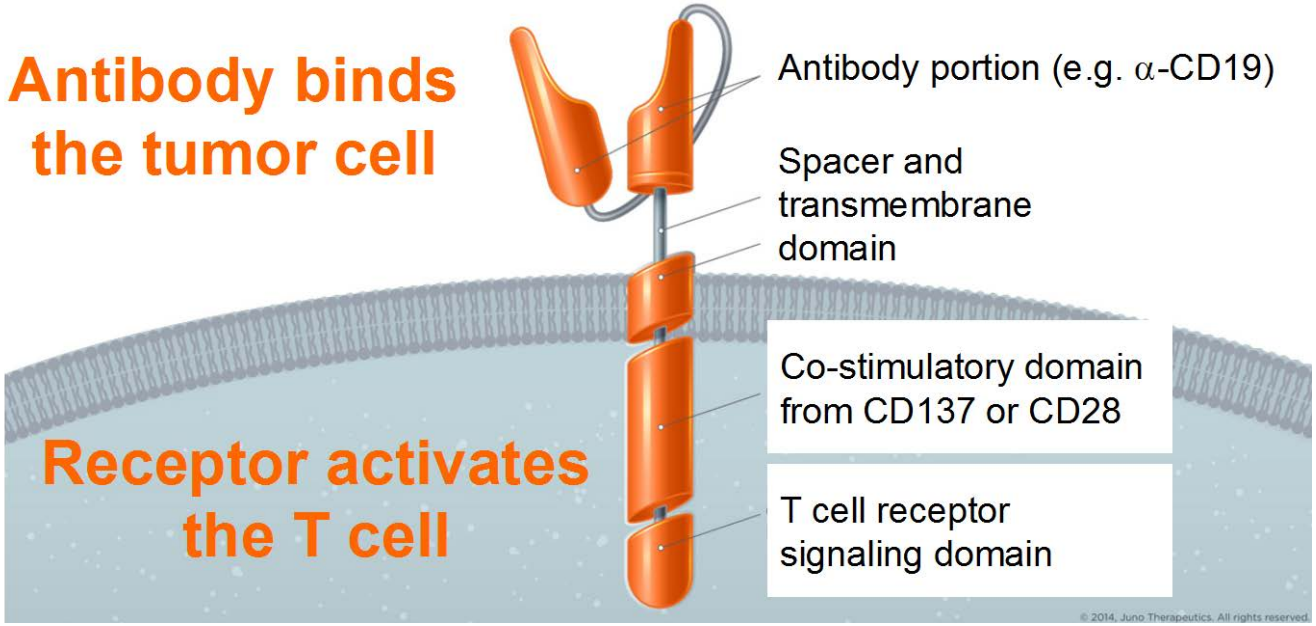


CD19 CAR-T cell clinical results



- 90% Complete Responses (67% sustained) in pediatric and adult B-ALL *(Davila, Sci Trans Med 2013; Maude, NEJM 2014)*
- 50-80% Objective Responses in lymphoma *(Kochenderfer, JCO 2014)*
- FDA approved for pediatric B-ALL (2017) and adult B cell lymphoma (2017, 2018)

CD19 CAR-T cell challenges



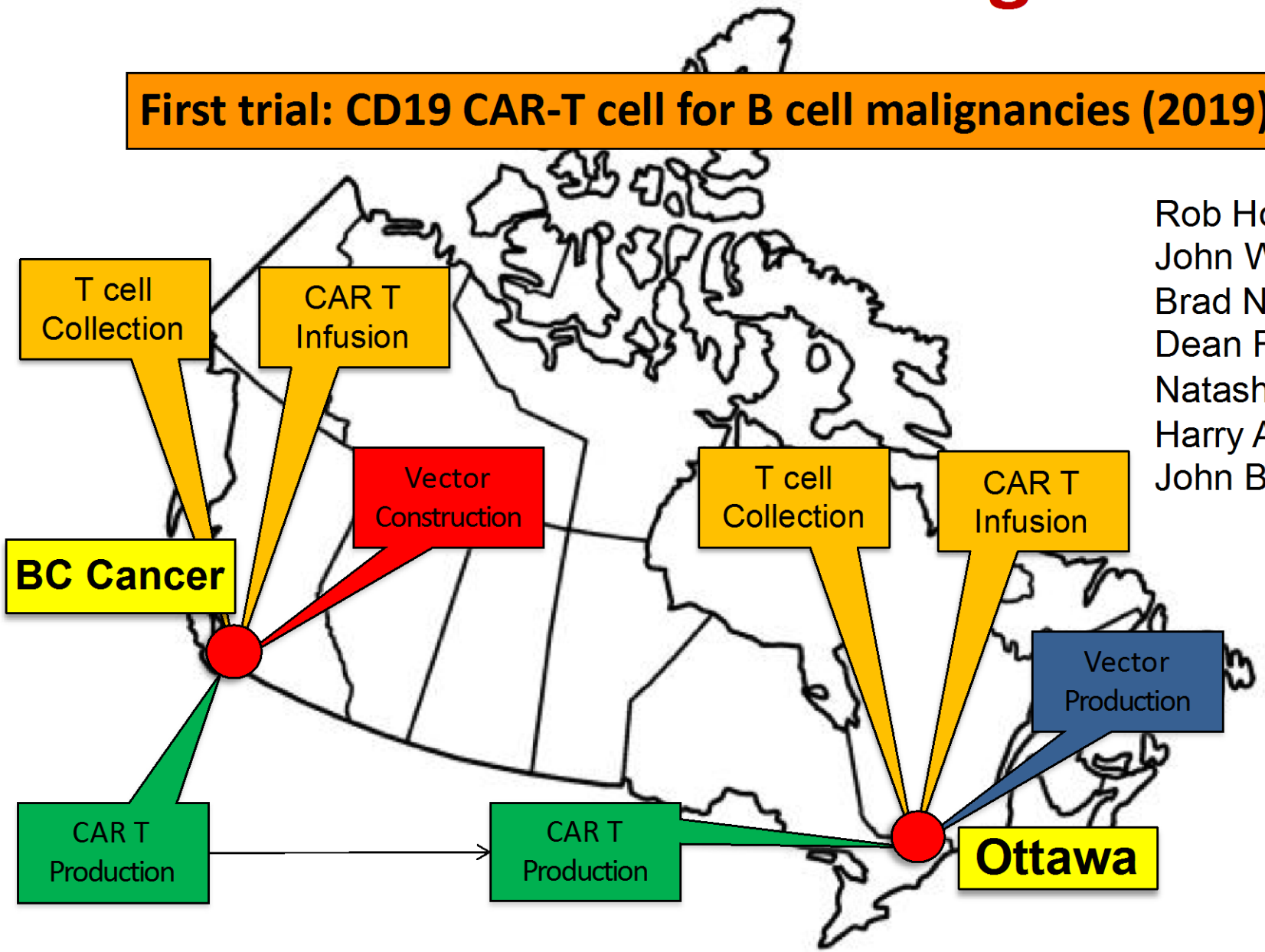
- Cytokine release syndrome
- Neurotoxicities of unclear etiology, with some fatalities
- Loss of healthy B cells for as long as the CAR-T cells are present
- About 1/3 of patients relapse, often with CD19-negative tumors
- Cost: US$400-500,000 per patient, just for the T cells

CAR-T Cell Wish List

- Lower toxicity
- Apply to other types of cancer
- Better penetration of solid tumours
- Fine-tuned control
- Failsafe stop mechanisms
- Affordable, feasible, sustainable

Canadian CAR-T Program

First trial: CD19 CAR-T cell for B cell malignancies (2019)



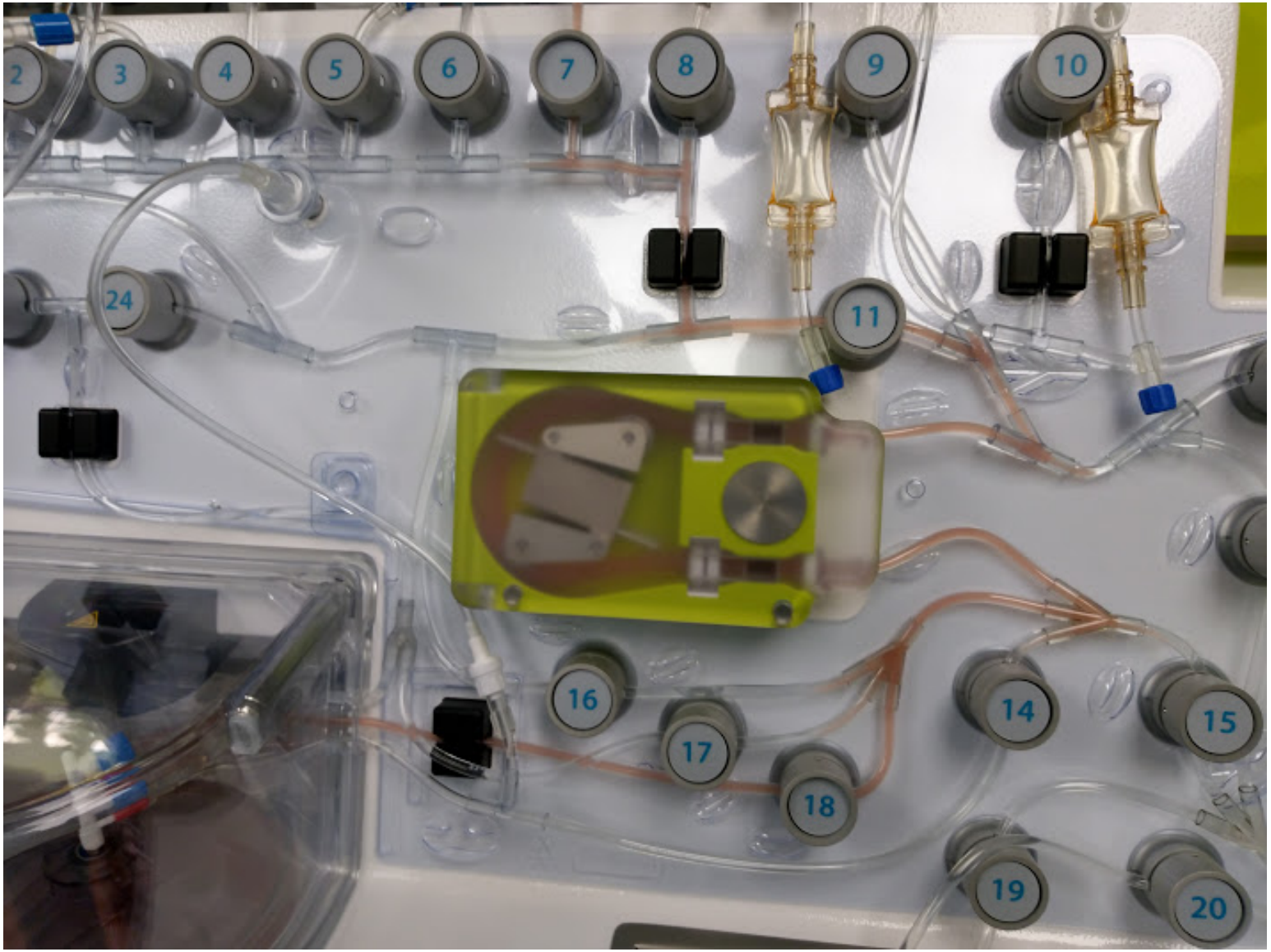
Rob Holt
John Webb
Brad Nelson
Dean Fergusson
Natasha Kekre
Harry Atkins
John Bell

Automated CAR-T Cell Manufacturing

BC Cancer's Deeley Research Centre, Victoria

Automated CAR-T Cell Manufacturing

BC Cancer's Deeley Research Centre, Victoria



The first cars…

….100 years later

BC CANCER
Provincial Health Services Authority

BC CANCER FOUNDATION
partners in discovery

Immunotherapy Program