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Immunotherapy 101 for GIST

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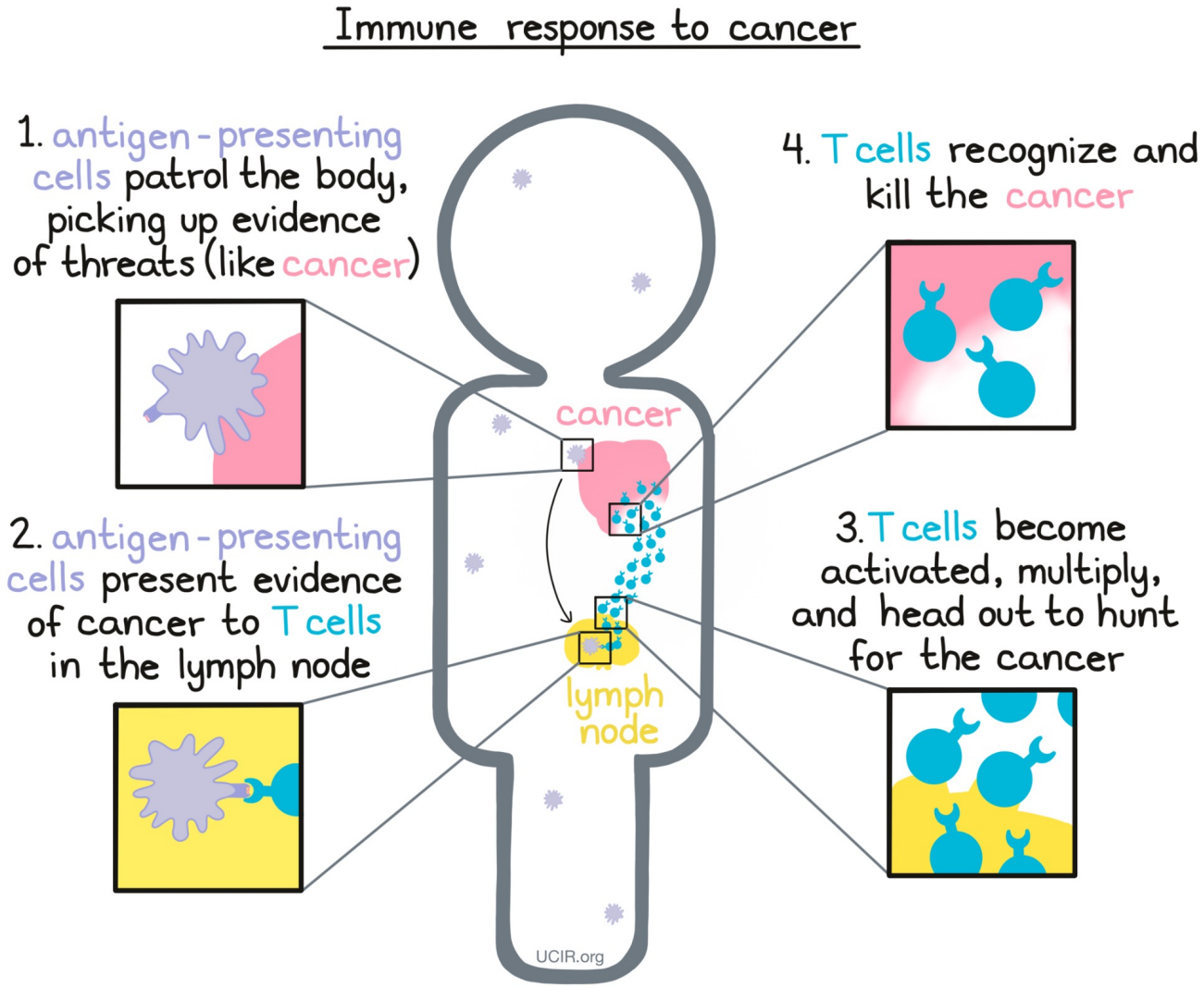
How does our immune system fight cancer?



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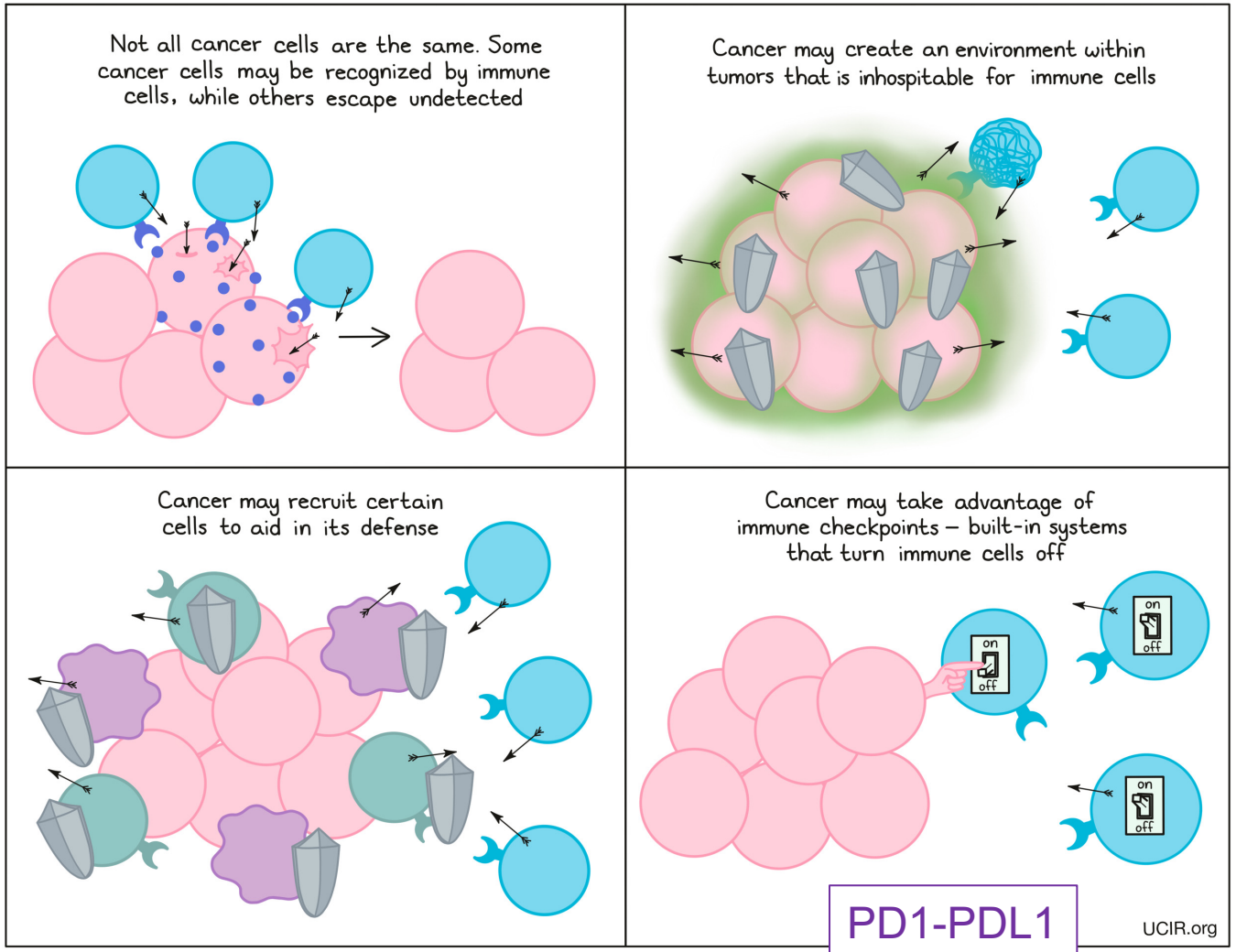
UCIR.org website –
AWESOME source for patient-friendly explanations of immune therapy!

Why does the immune system fail to kill off cancer?

- Cancer cells look more like “ourselves” than viruses or bacteria (foreign)
- The more genetically “broken” or mutated the cancer cell is, the more funny-shaped proteins get produced by the cancer cell and the better chance to be recognized



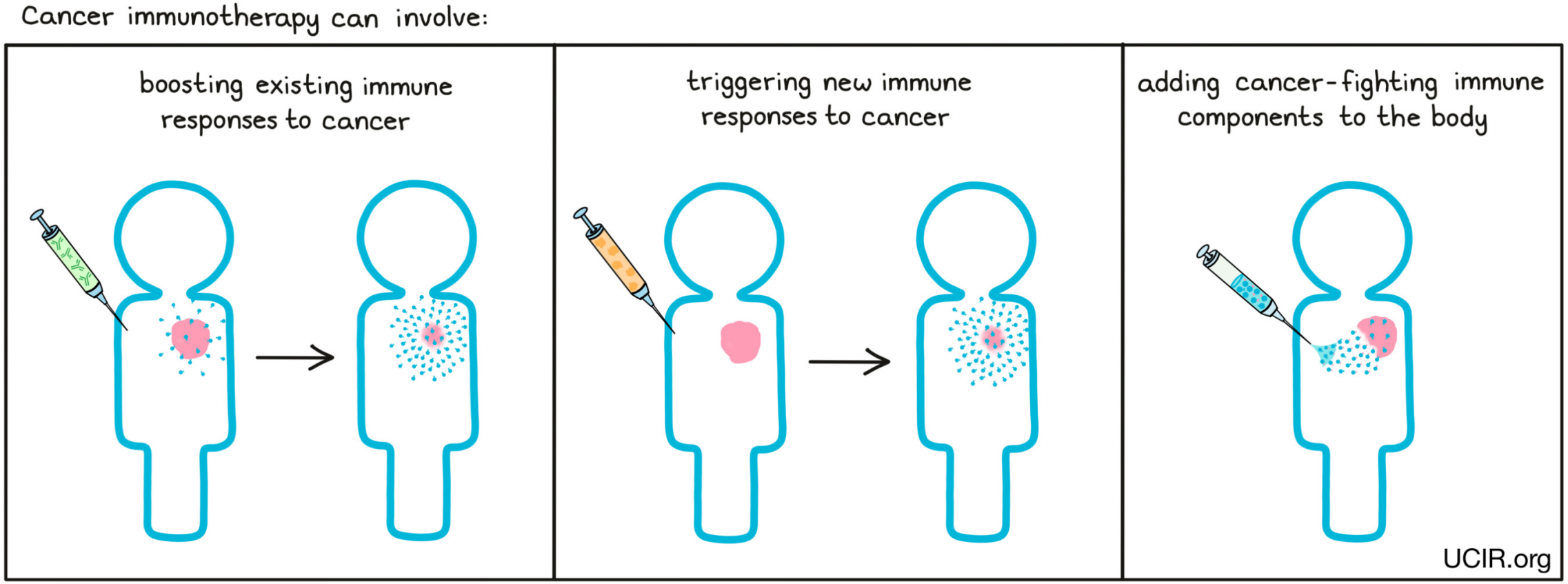
PD1-PDL1
CTLA-4
others

Goals for treatment

So for MOST patients – immune therapy needs to address:

- Lack of “foreign-ness”– not enough, or the wrong antigens
- The immune cells specific for the tumor are not able to get into the tumor
- Tumor-specific immune cells are shut down by other suppressive factors
- How do we try to fix these issues?

How does cancer immunotherapy work?



Checkpoint protein inhibitors

Vaccines, Virus therapies, Chemotherapy/radiation

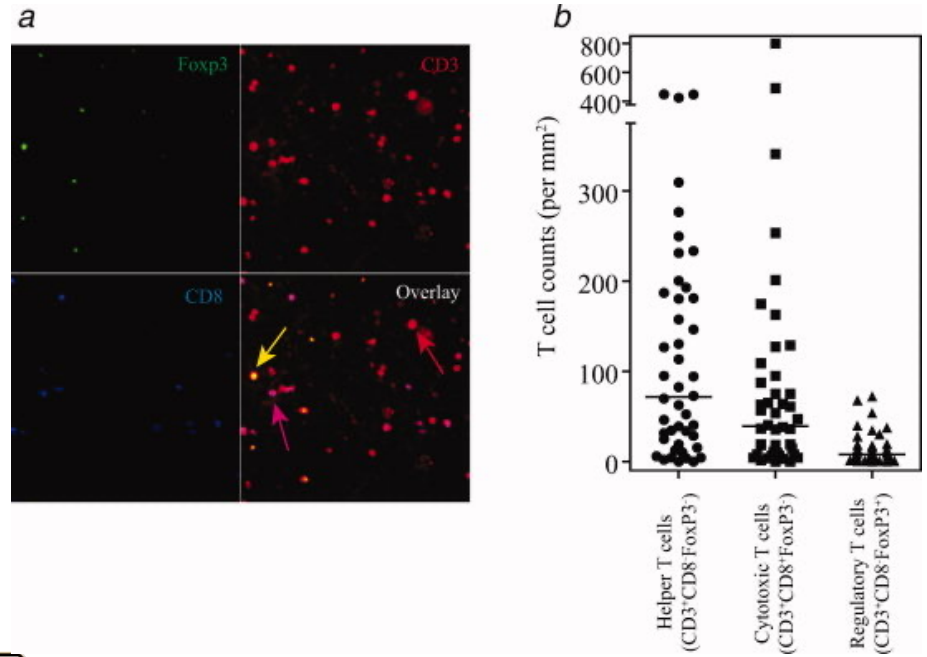
Cellular therapy

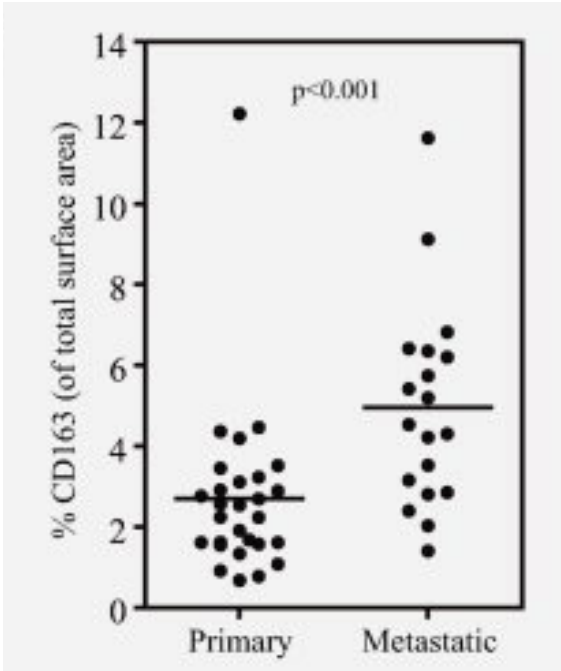
What immune cells are in GIST?

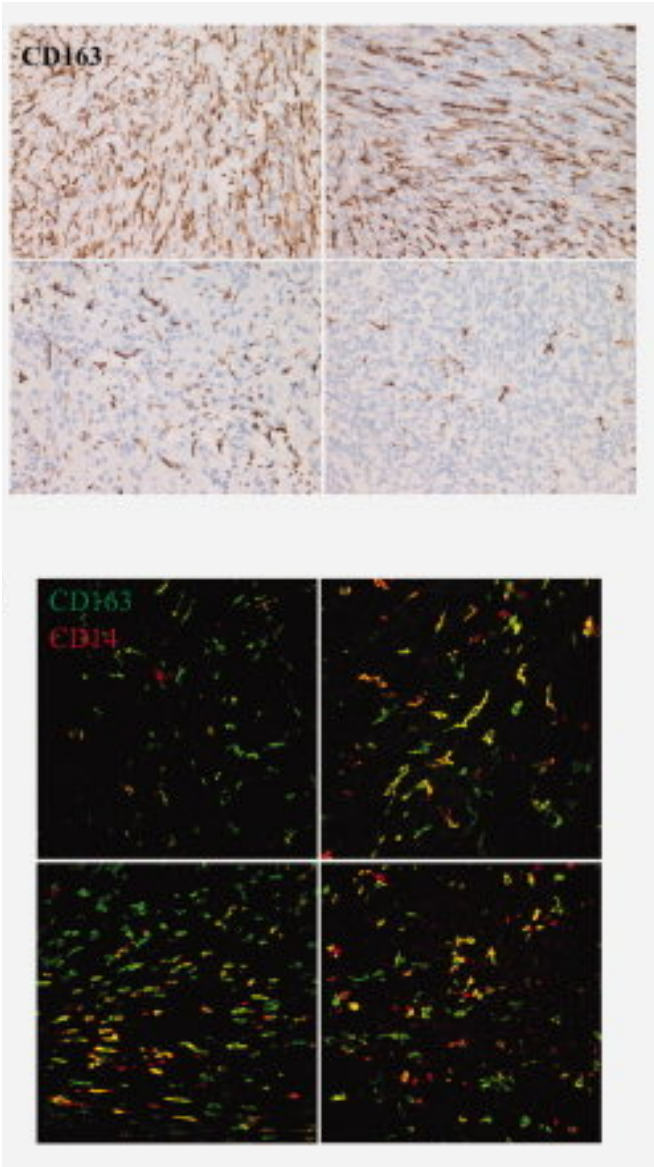
A lot!

- T cells
- Macrophages
- NK cells

- Regulatory T cells
- Macrophages







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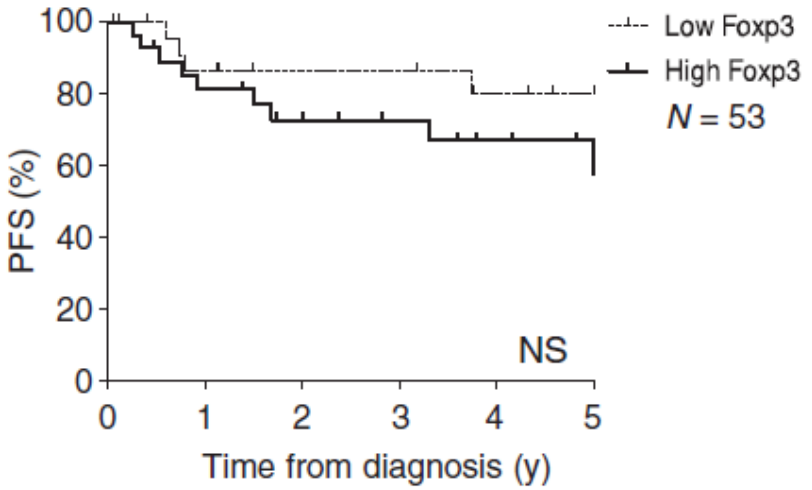
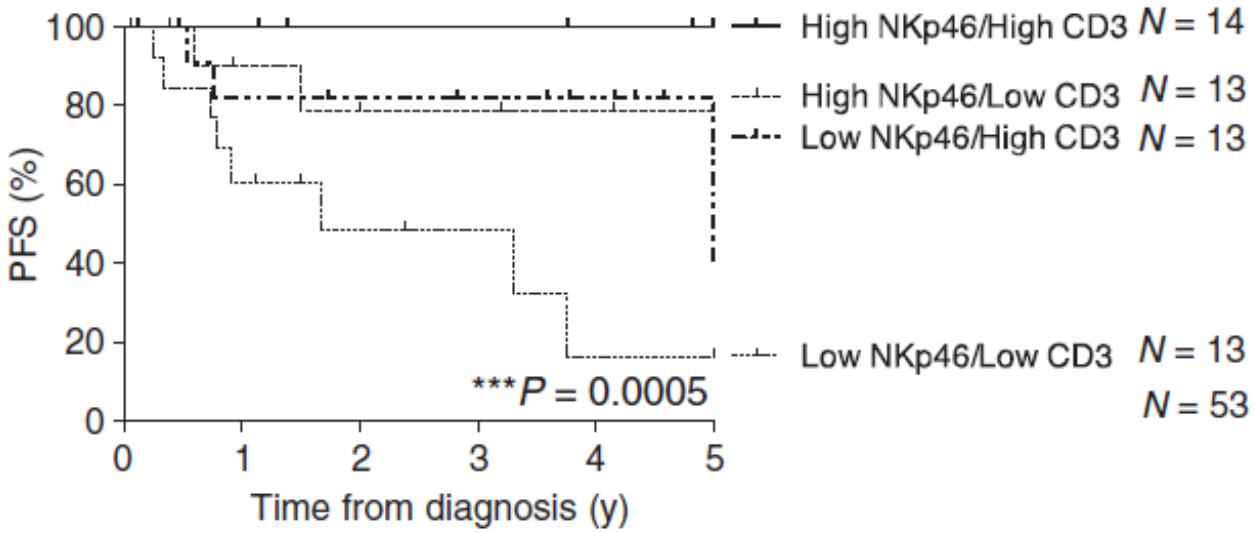
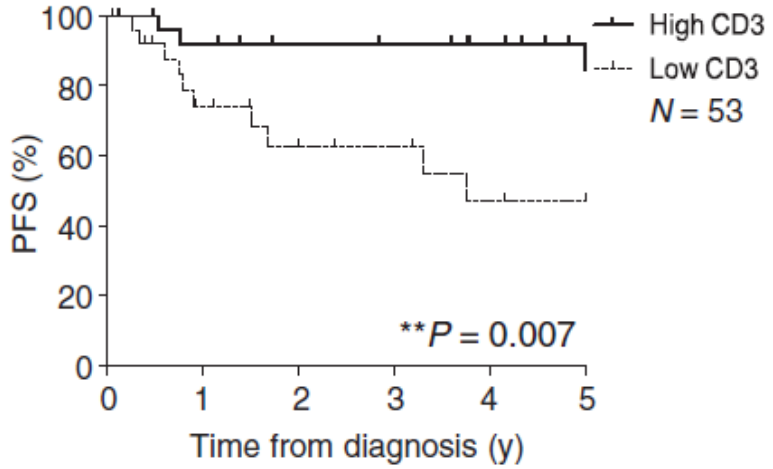
Tan et al, Cancer Gen Ther 2017
Van Dongen et al, Int J Cancer 2010

What immune cells are in GIST?

- In localized GIST, improved PFS with
  - Low T regs
  - High CD3+ infiltrates
  - High CD3+ and NK cells



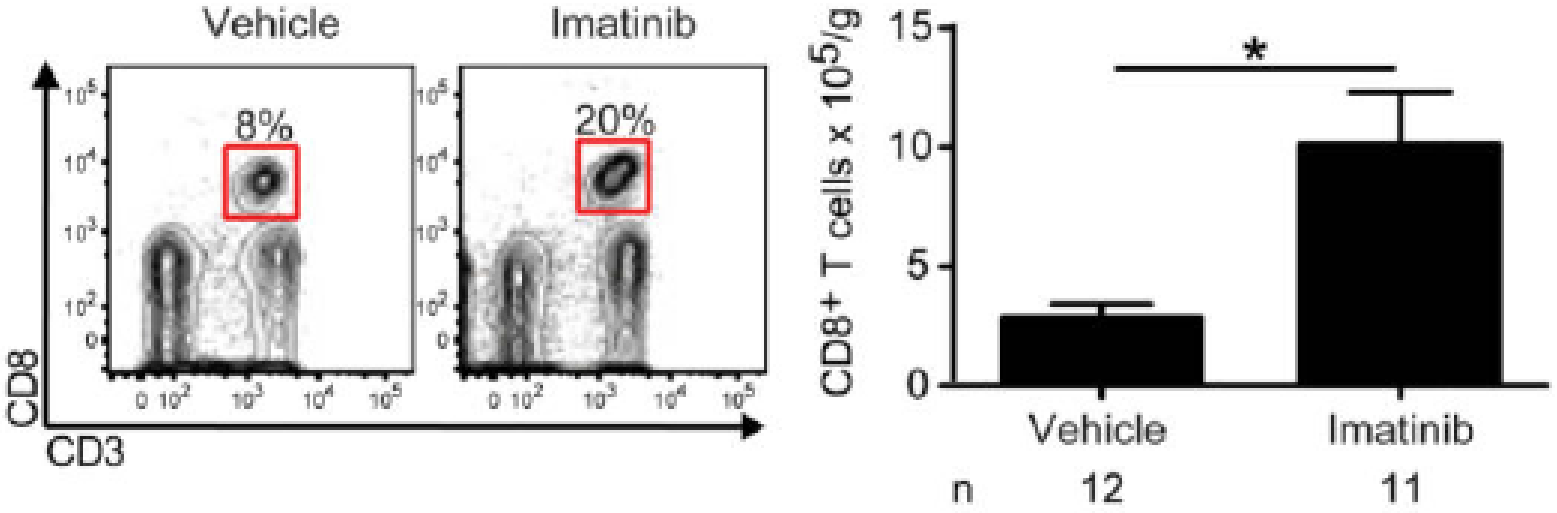




Rusakiewicz et al, Cancer Res, 2013.

Effect of imatinib on immune cells

- Increases CD8+ cytotoxic T cells
- Decreases suppressive regulatory T cells
- Decreases production of IDO (suppressive cytokine)
- Increases PD-1 and PD-L1 expression on immune and tumor cells
- Reverts back with resistance to imatinib…



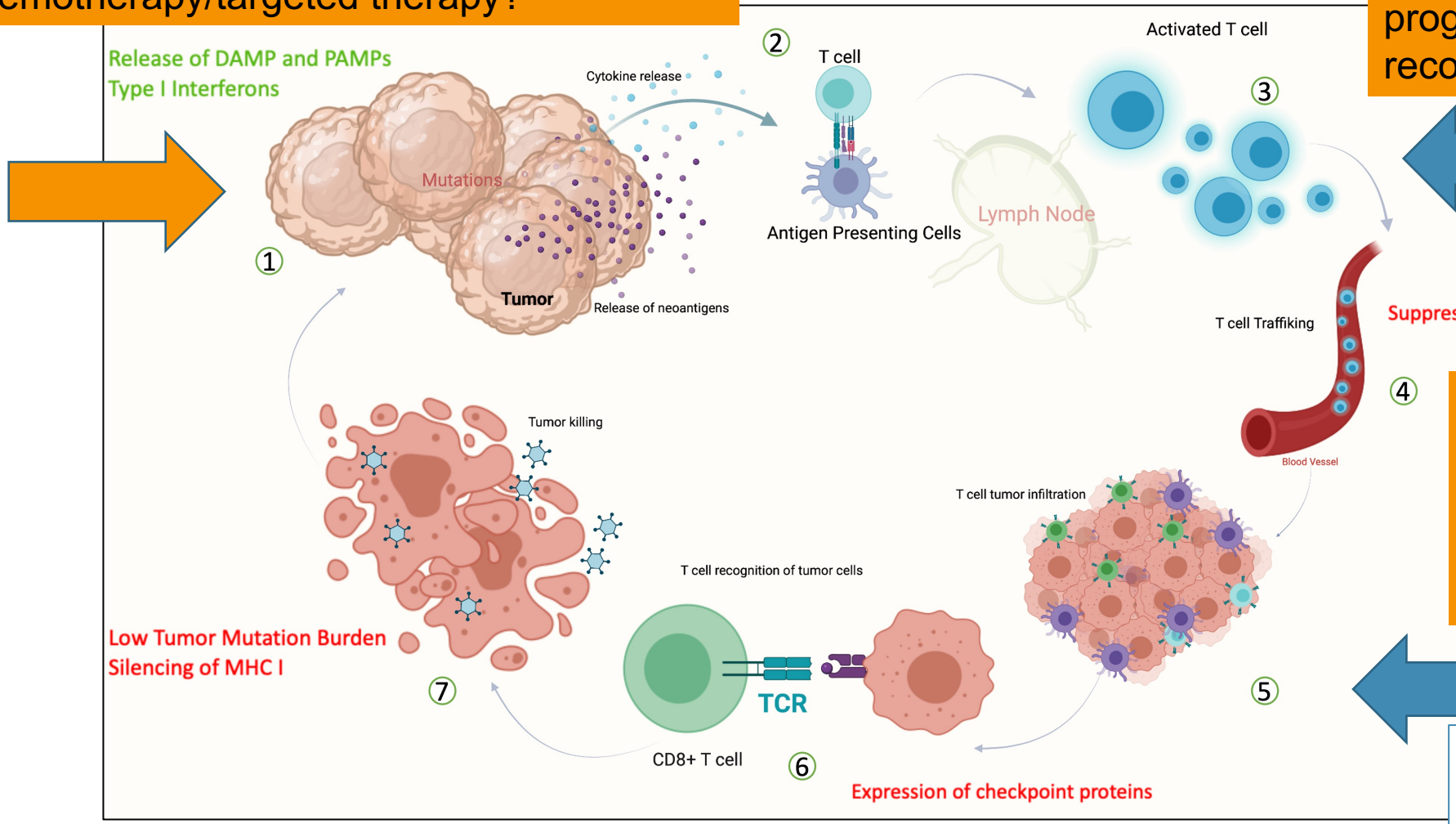
Balachandran et al, Nat Med 2011
Munn et al, Trends Immunol 2013
Seifert et al, Clin Canc Res, 2016

The immune system is recognizing SOMETHING about GIST…

- Low mutations but immune cells are there
  - Quality over quantity…
- Imatinib might work not just on slowing the growth of GIST but potentially through immune activities
- Can we harness/intensify the immune system?

How to boost or bypass immune recognition of cancer cells

Chemotherapy/targeted therapy?



Give T cells already programmed to recognize targets

Target key pathways that promote immune cell "stalling" (suppression in the tumor environment)

Checkpoint inhibitors
IDO inhibitors
VEGF inhibitors

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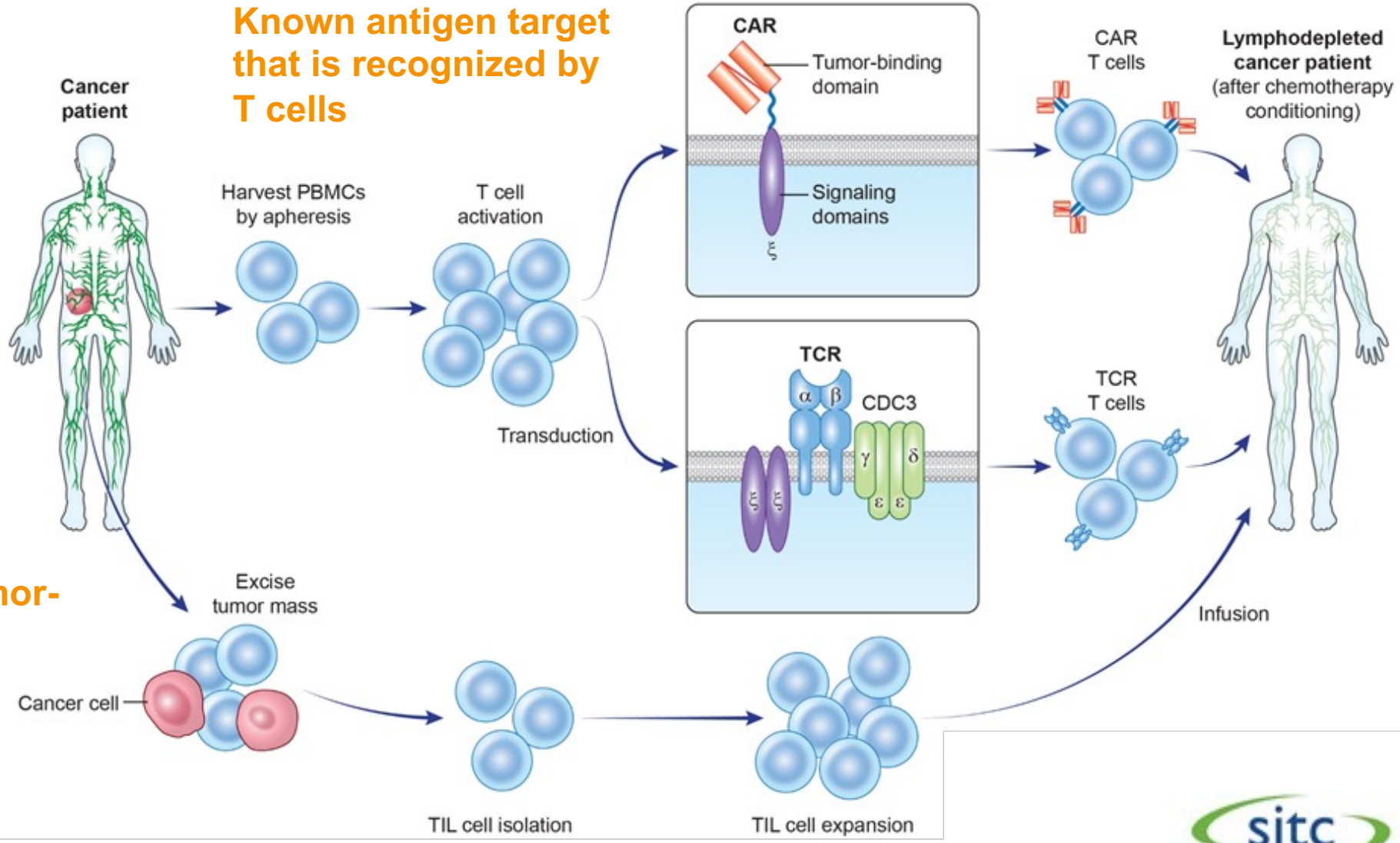
Florou & Wilky, Cancer Drug Res, 2022

Future directions – adoptive cellular therapies

CAR-T cells
Engineered T cells
TIL therapy

Known antigen target that is recognized by T cells



Presumed tumor-specific T cell population

Immune therapy in GIST – summary…

- Cellular therapies – need more targets
- Some efforts to develop KIT CAR-Ts, but on other normal cells as well – risks of toxicity…
- Not ready for primetime yet

- Overall takehome –

From immunology perspective – immune therapy should help in GIST… but HOW and for WHOM is still a mystery.

- Now to hear about specific efforts for immunotherapy in GIST…

THANK YOU…

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