

What's Next for Cancer Immunotherapy?

Andrew L. Coveler, MD

Associate Professor, University of Washington

Associate Member, Fred Hutch

Disclosures

- Research Funding
 - AbGenomics, FivePrime, Halozyme, Seattle Genetics, Merck, NuCana,
- Consulting
 - Abbvie
- I **will** be discussing non-FDA approved indications during my presentation.

In 2016



Immunotherapy on the Horizon

Andrew L. Coveler

Assistant Professor of Medicine, Division of Oncology

University of Washington

Assistant Member

Fred Hutchinson Cancer Research Center

Image: NASA.gov



Checkpoint Blockade

- Hodgkin Lymphoma
- Head and Neck Cancer
- Gastric Cancer
- Colon Cancer



CAR T Cells

- Leukemia
- Lymphoma



Then and Now



Immunotherapy on the Horizon

Checkpoint Blockade

- Mostly PD1
- Some PDL1

Now

- CTLA4 + PD1

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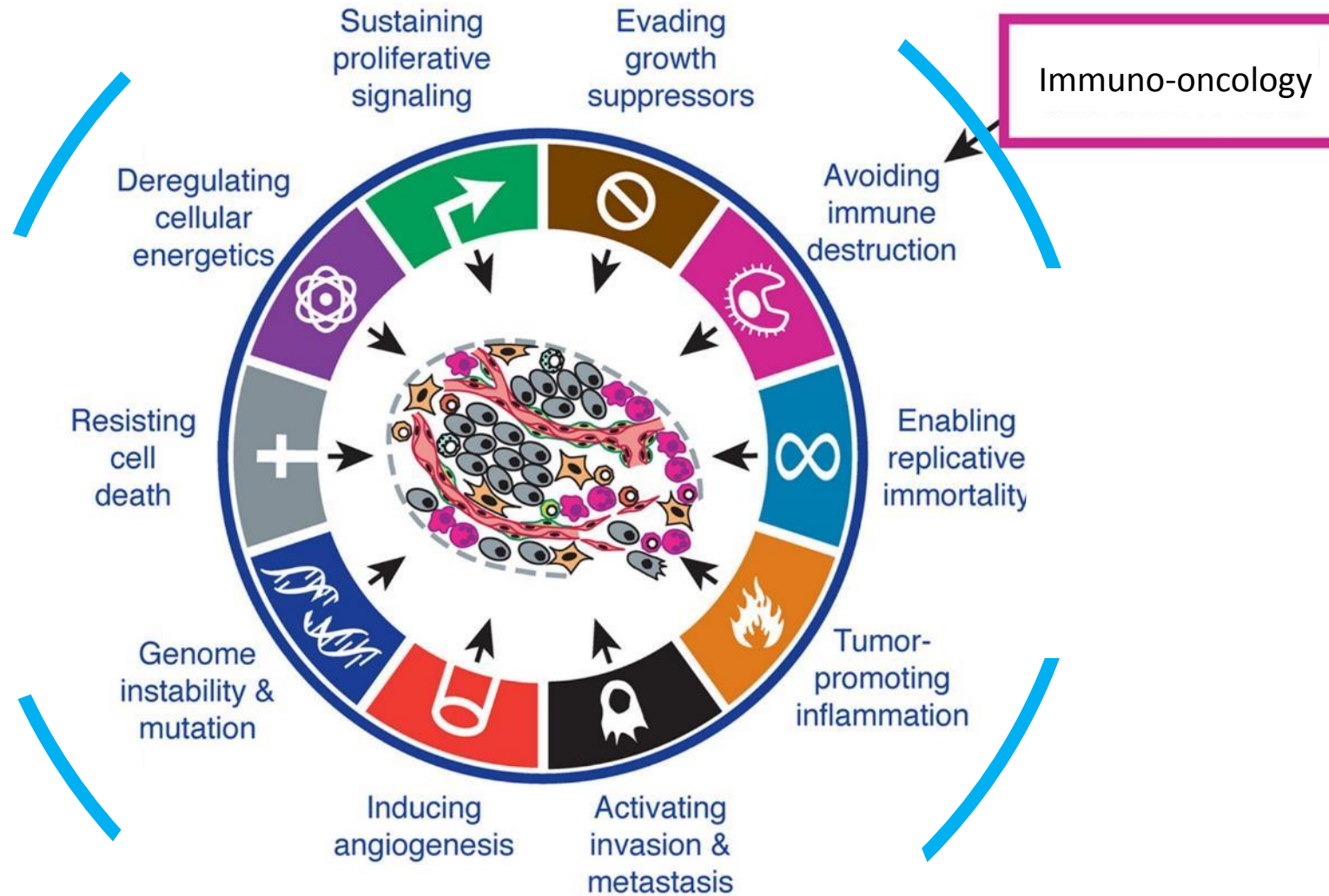
Assistant Member

Fred Hutchinson Cancer Research Center

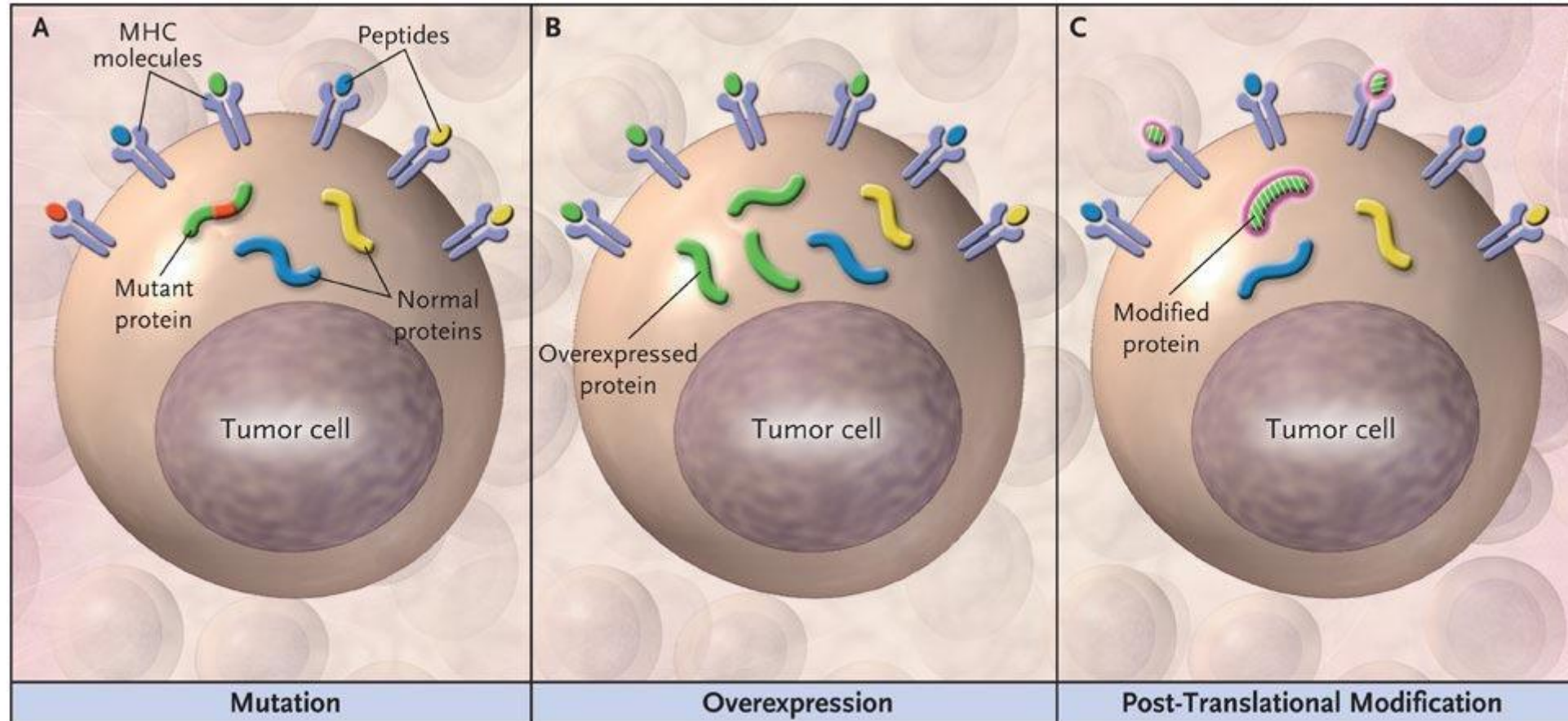
Image: NASA.gov



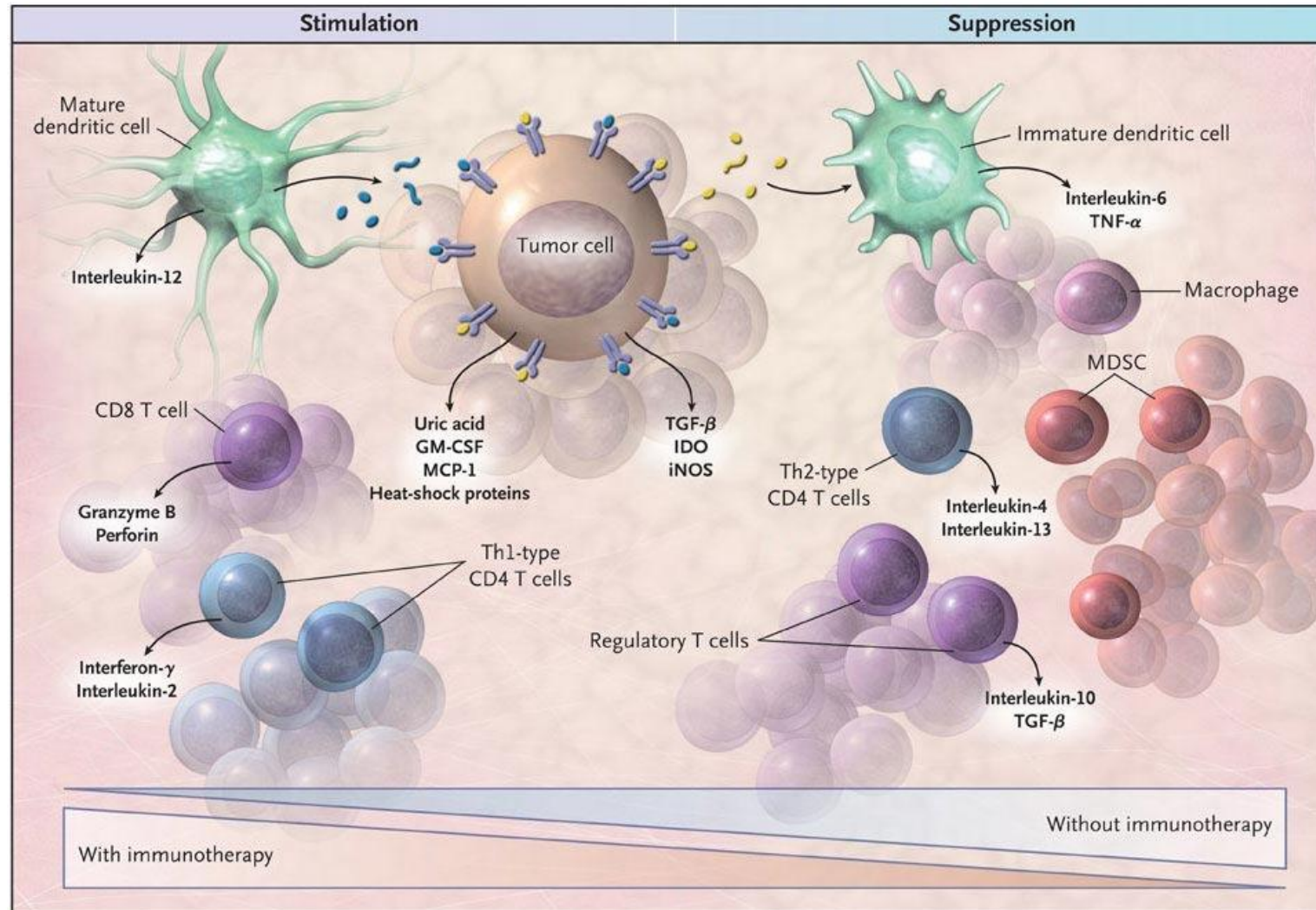
Hallmarks of Cancer



2008



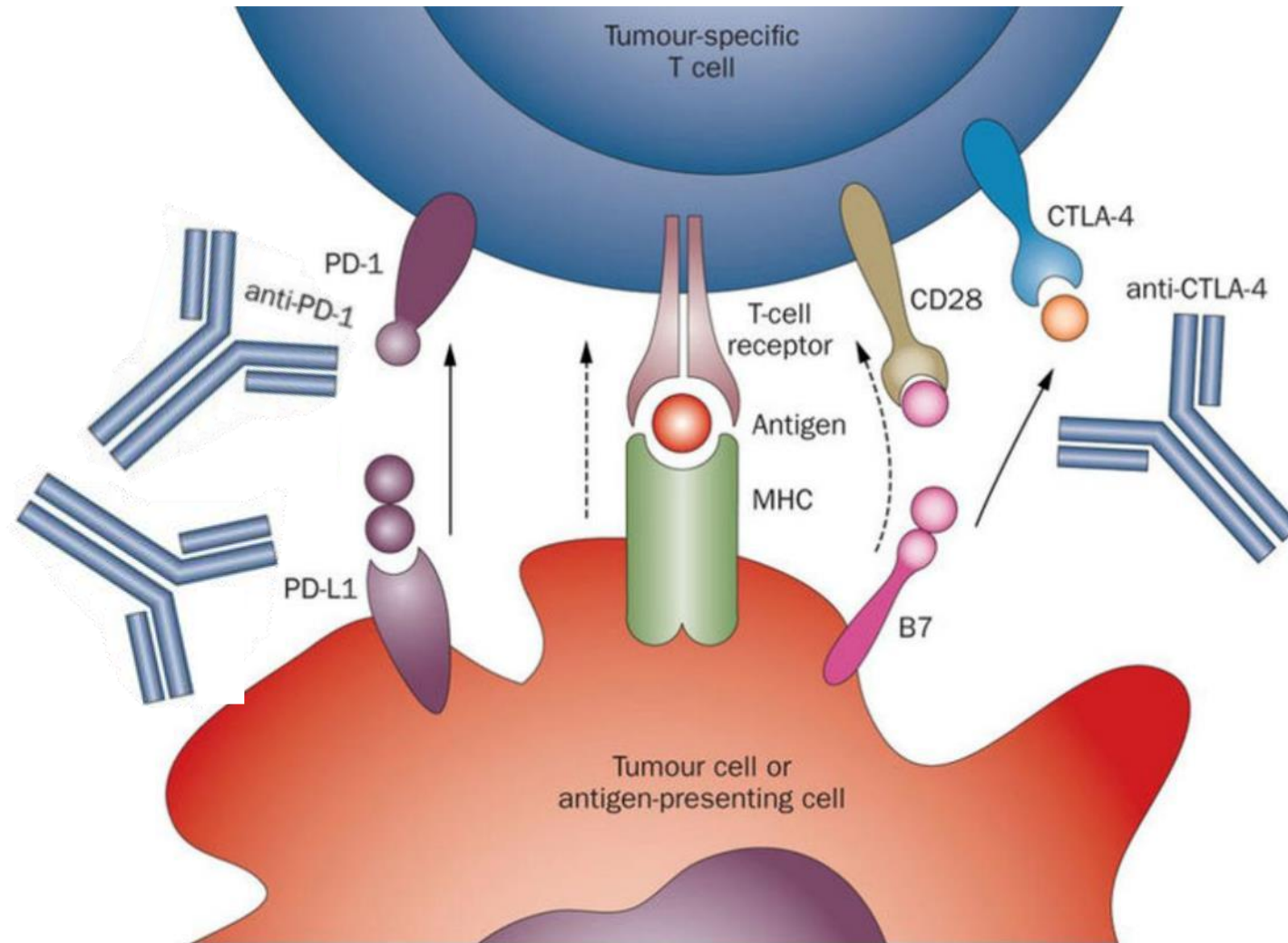
2008



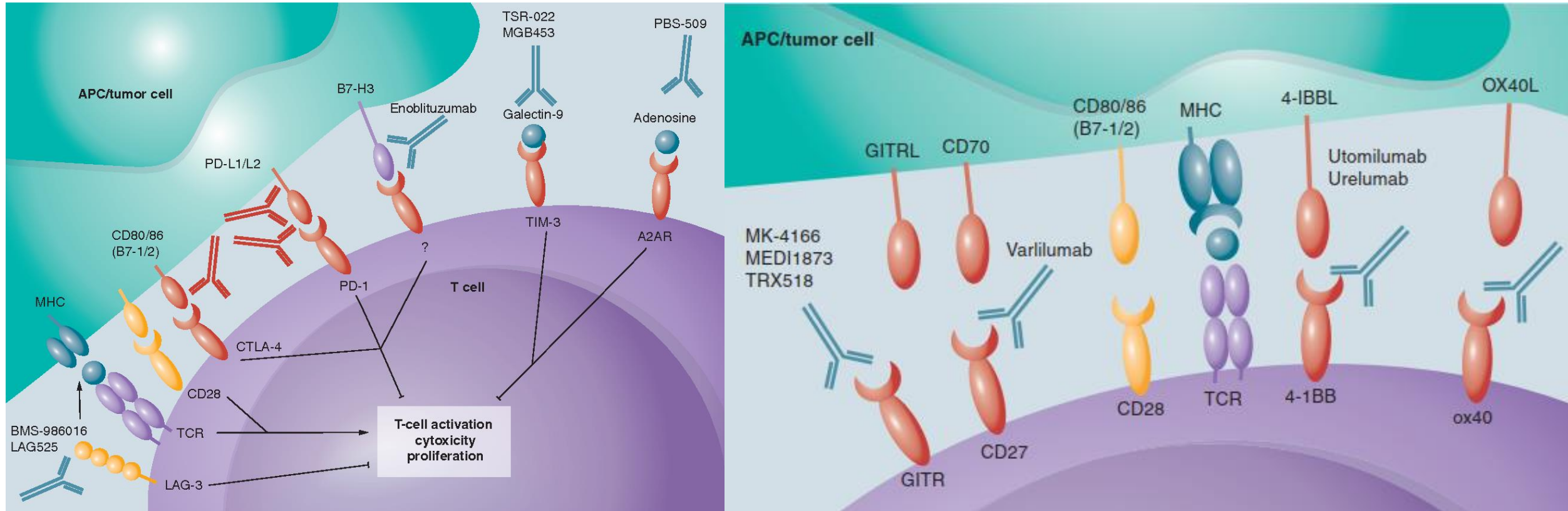
Future Immunotherapy Therapeutics

- **Checkpoint - Combinations**
 - **Checkpoint Inhibitors**
 - Checkpoint Agonists
- **Biologics**
 - Microbiome
 - Oncolytic Viral Therapy
 - Cellular Therapy (CAR T, CAR NK)
- **Antibody**
 - Bispecific
 - Antibody Drug Conjugates
- **Standard Combinations**
 - Radiation
 - Chemotherapy

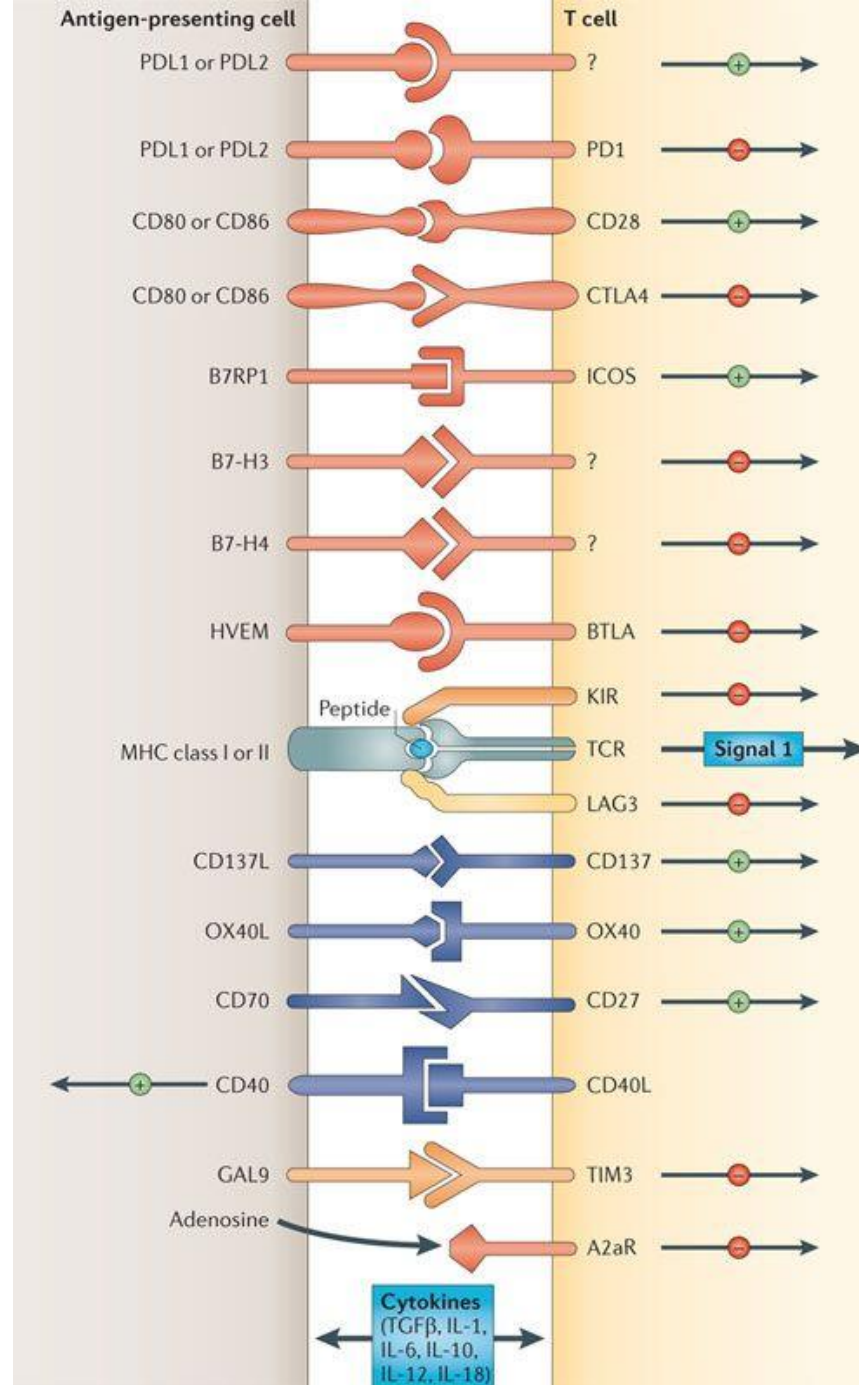
2014



2018



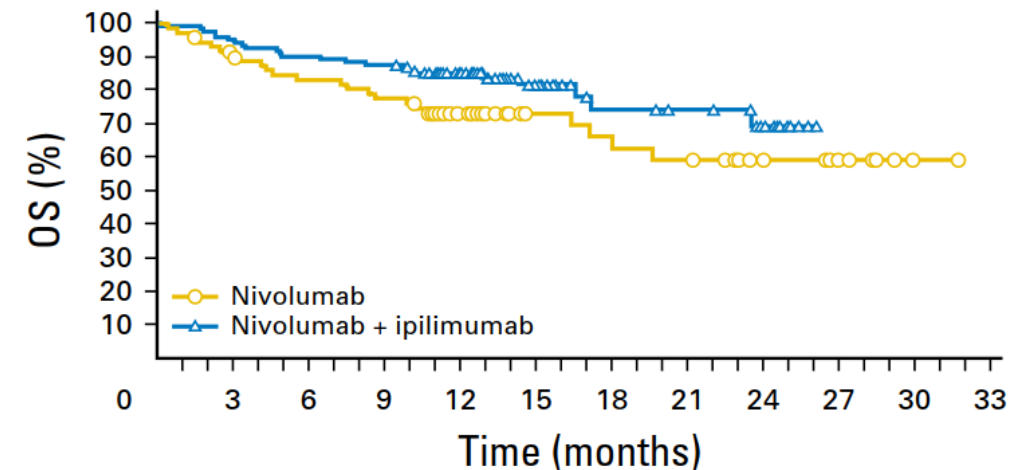
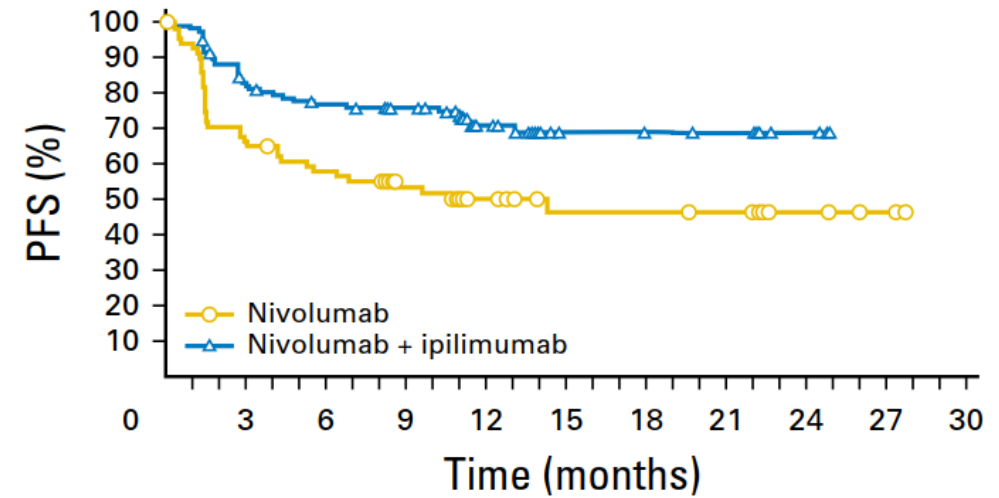
Co-Inhibitor | Co-Stimulator



Inhibitors: (CTLA4 + PD1)

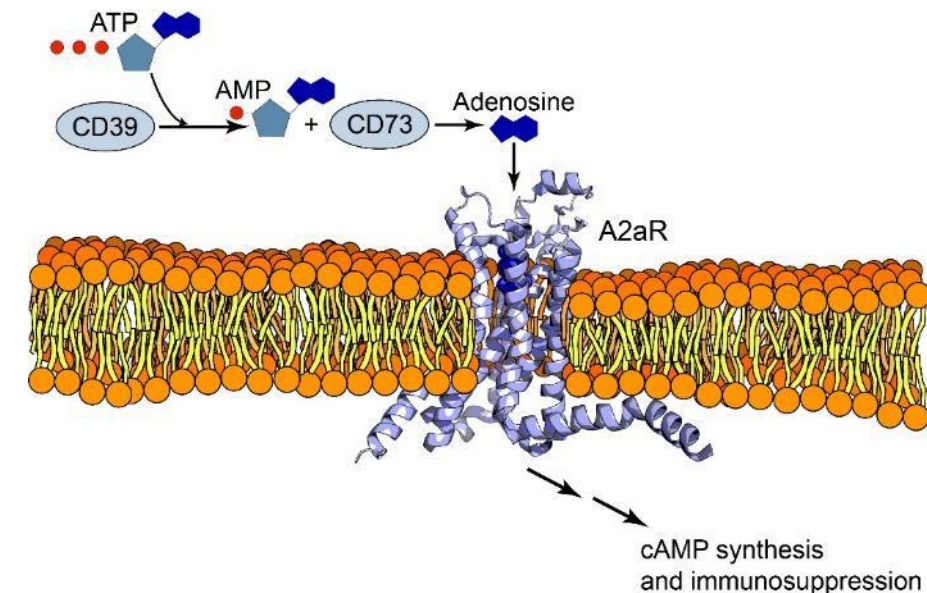
Ipi + Nivo -> Nivo is MSI CRC

- nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q3 weeks x4 then nivolumab 3 mg/kg q2 weeks
- 119 patients, mFU 13.4 months
 ORR 55% (95% CI, 45.2 to 63.8),
 DCR > 12 weeks 80%.
- ORR for pembrolizumab 30%



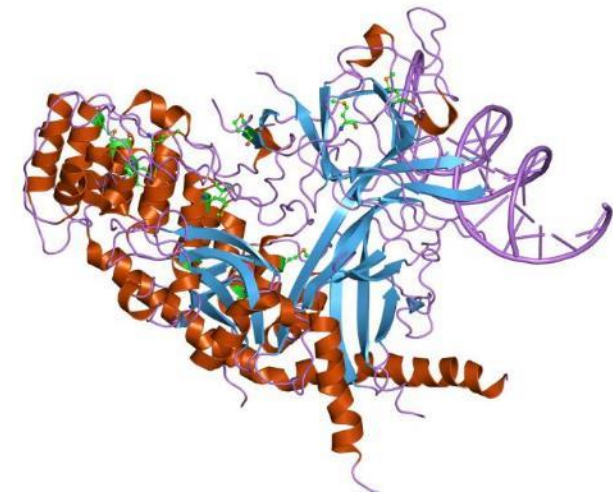
Inhibitor: Adenosine A2AR

- Glycolysis leads to excessive adenosine monophosphate
- CD73 on tumors cells turns adenosine monophosphate to adenosine
- Adenosine binds A2AR on T and NK cells
- Inhibiting NK, CD8, CD4 Th1 cells
- Maintaining tissue inflammation
- NCT02403193: PBF-509 + PDR001 in NSCLC



Inhibitor: Lymphocyte Activating Gene-3 (LAG-3)

- Member of immunoglobulin superfamily
- Expressed on B cells, NK cells, TILs, some T Cells
- Co-inhibitory receptor
- Low levels on naïve CD8 T cells, but increases with antigenic stimulation
- It binds MHC II and inhibits TCR-induced Ca^{++} thus decreasing effector functions of CD8 T cells.
- NCT02460224: LAG525 + PDR001 in Advanced Malignancies



Inhibitor: T-cell Immunoglobulin & mucin-3 (TIM-3)

- Is expressed on activated T cells, NK cells, Monocytes
- Binding galectin-9 it facilitates immune tolerance.
- TIM-3 knockout mice develop autoimmunity (less than PD-1/CTLA4 knockout mice)
- TIM-3+ TIL co-express PD-1
- NCT02817633, NCT02608268 has TSR-022 or MGB-453 in combination with PD-1 inhibition for advanced solid tumors



3 Tims Cook, Curry, Allen (Internet)

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- Chemotherapy

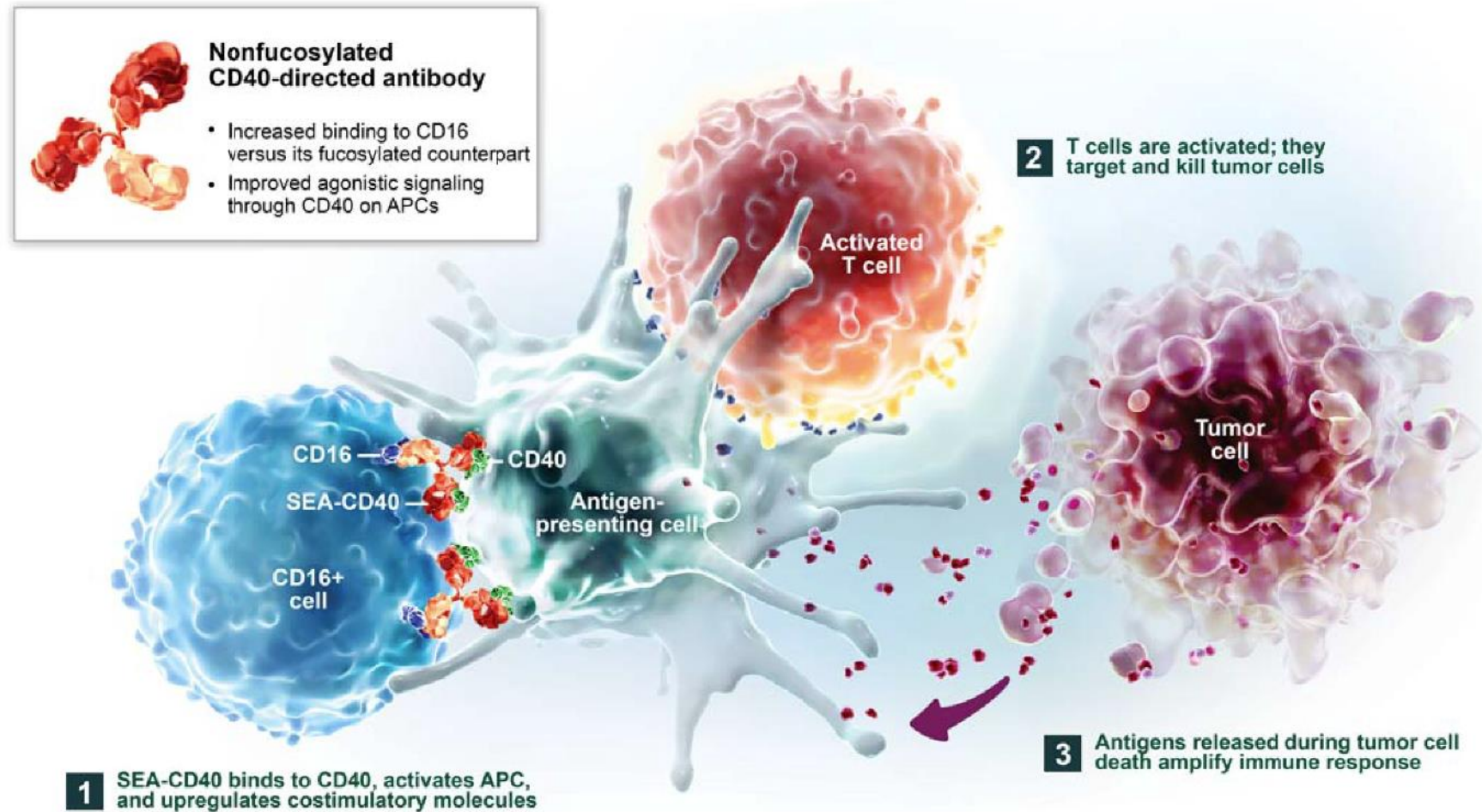
Co-Inhibition to Co-Stimulation

- Success of nivolumab, pembrolizumab and ipilimumab placed a spotlight on check point co-inhibitors
- Co-stimulators are showing promise also....
- Increase the activity of exhausted CD8 T cells

Stimulator: CD40

- Is expressed by immune, hematopoietic, epithelial, and other cells
- Key regulator of immune responses via its expression on antigen-presenting cells (APCs), B lymphocytes, dendritic cells, and monocytes
- Induces tumor regression via an indirect effect of immune activation and a cytotoxic effect on CD40-expressing tumors
- Expressed on a majority of solid tumors and nearly 100% of B-cell malignancies
- As a co-stimulatory receptor expressed by normal immune cells, tumor expression is not required for CD40 to be an effective target

SEA-CD40 Proposed Mechanism of Action



SEA-CD40 is an investigational agent, and its safety and efficacy have not been established. ©2018 Seattle Genetics, Inc. All rights reserved.

Stimulator: GITR

Glucocorticoid-induced TNFR family related protein

- Expressed on activated T cells, NK cells, B cells
- When bound promotes proliferation and activation
- GITR agonists deplete regulatory T cells
- GITR agonists promote effector function
- NCT02132754:
 anti-GITR plus
 pembrolizumab in melanoma

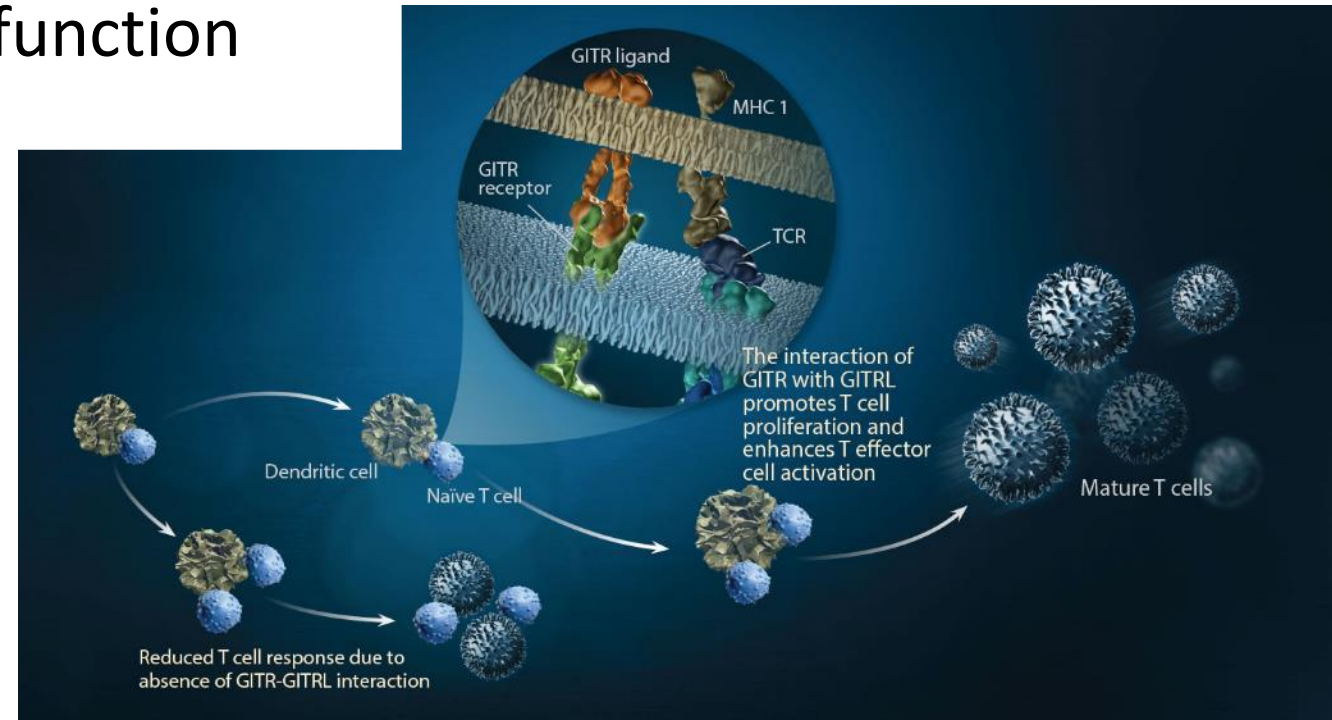


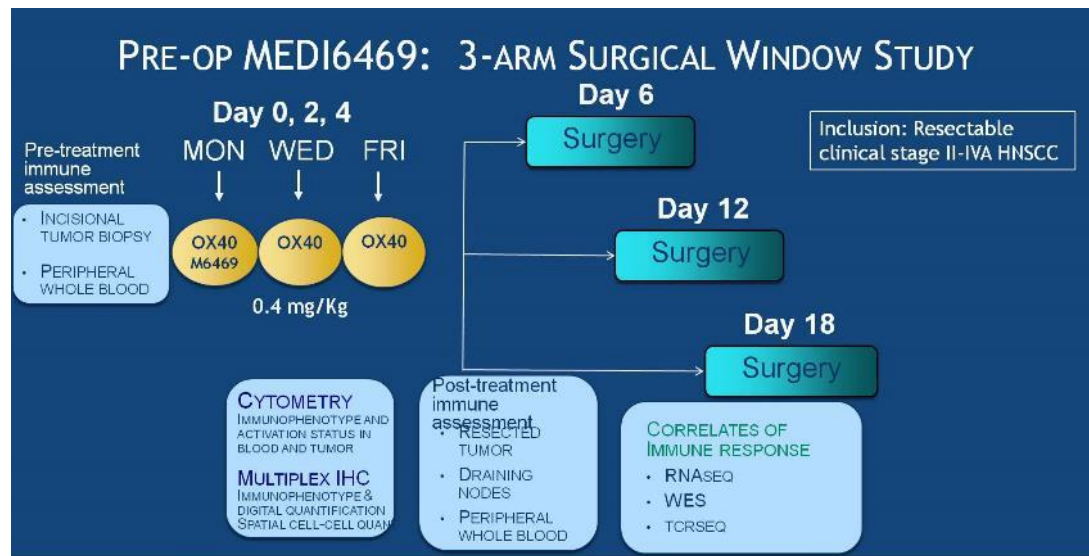
Image: <http://www.amgenoncology.com/science/t-cell-modulation-gitrl.html>

Stimulator: 4-1BB

- Expressed on activated CD8 T cells, CD4 T helper cells, B cells
- Induces T-cell proliferation
- Enhances T-cell effector function
- Inhibits activation induced cell death, upregulates antiapoptotic genes
- A Phase II trial was stopped as was many other studies secondary to severe liver toxicity. New trials are undergoing.

Stimulator: OX40

- Member of the TNFRsf and primarily expressed on CD8+ & CD4+ T cells
- In a Phase I trial, 12 pts had regression with No PRs or CRs.
- **OX40 and PD1 and CTLA-4 expressed on H&N TILs**



PRESENTED AT: 2018 ASCO ANNUAL MEETING

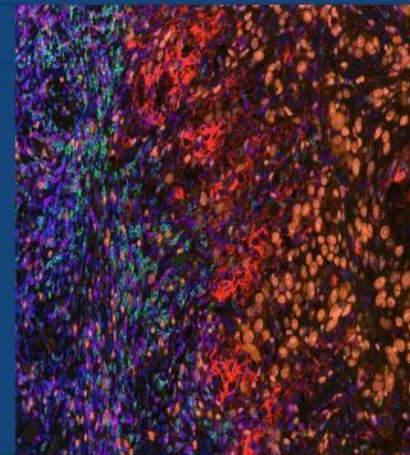
#ASCO18
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PRESENTED BY: R. Bryan Bell

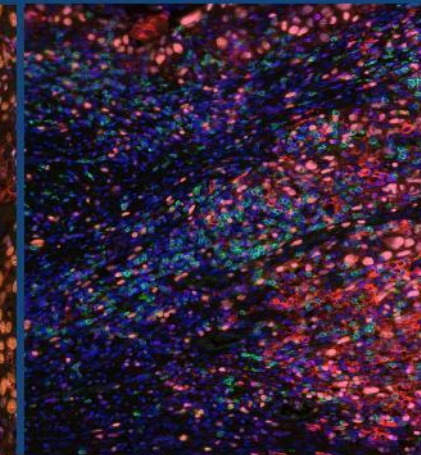
HNOX07, Day 18, Oral tongue, HPV-

Ki67 = orange PD-L1 = red
 CD8 = green CD3 = purple

PRE



POST



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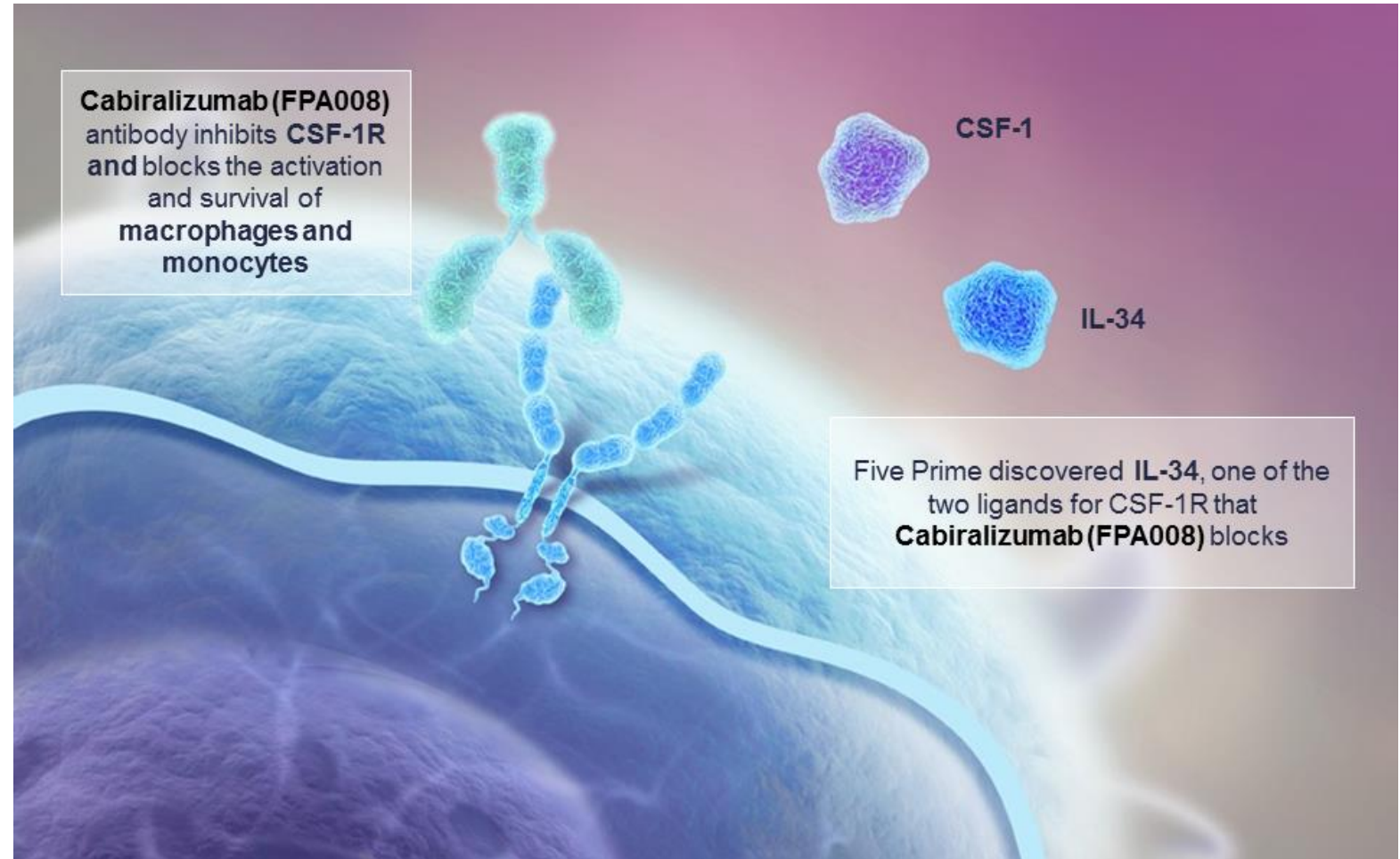
Z. Feng, C. Ballesteros-Merino, C. Bifulco, B. Fox

Stimulator-ish: CSF-1R

NCT03336216
Cabiralizumab
+ Nivolumab
+/- Chemo

For pancreas cancer
patients

Decrease TAMs



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Biomarker or Therapy: Microbiome

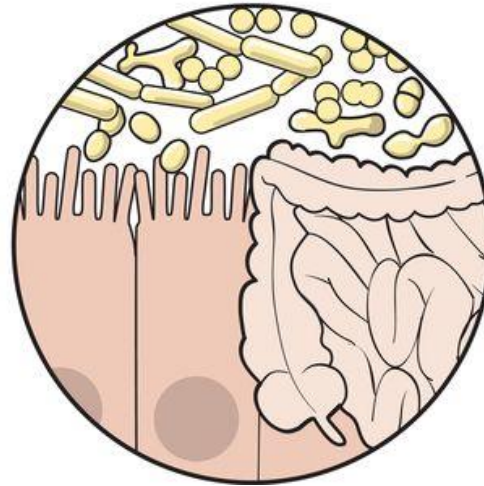
Cancer therapies

Anticancer treatment modalities and co-medications (such as antibiotics) affect the integrity of the epithelial barrier.



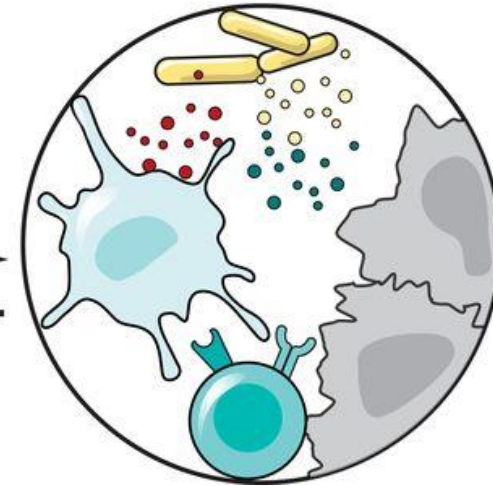
Microbiome

Gut-resident commensals interacting with epithelial, stromal, endocrine, neural, immune intestinal cells to regulate barrier functions and whole-body metabolism.



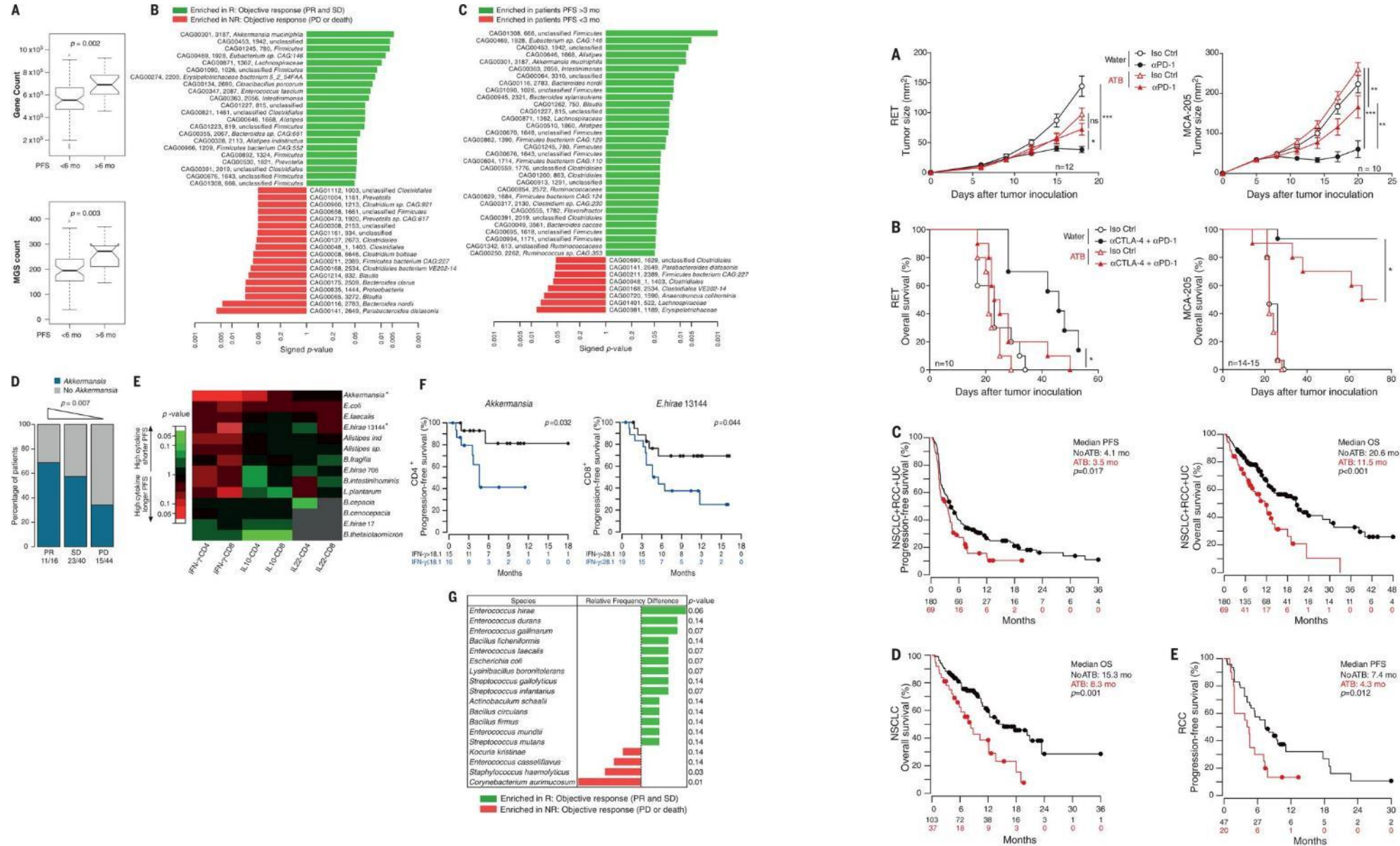
Immune responses

The gut microbiota has systemic effects throughout the meta-organism via secretion of anti-inflammatory cytokine/chemokines, metabolites, antimicrobial and neuropeptides.



Certain Bacteria Predict Response

Antibiotics compromise PD-1 Blockade in Mice

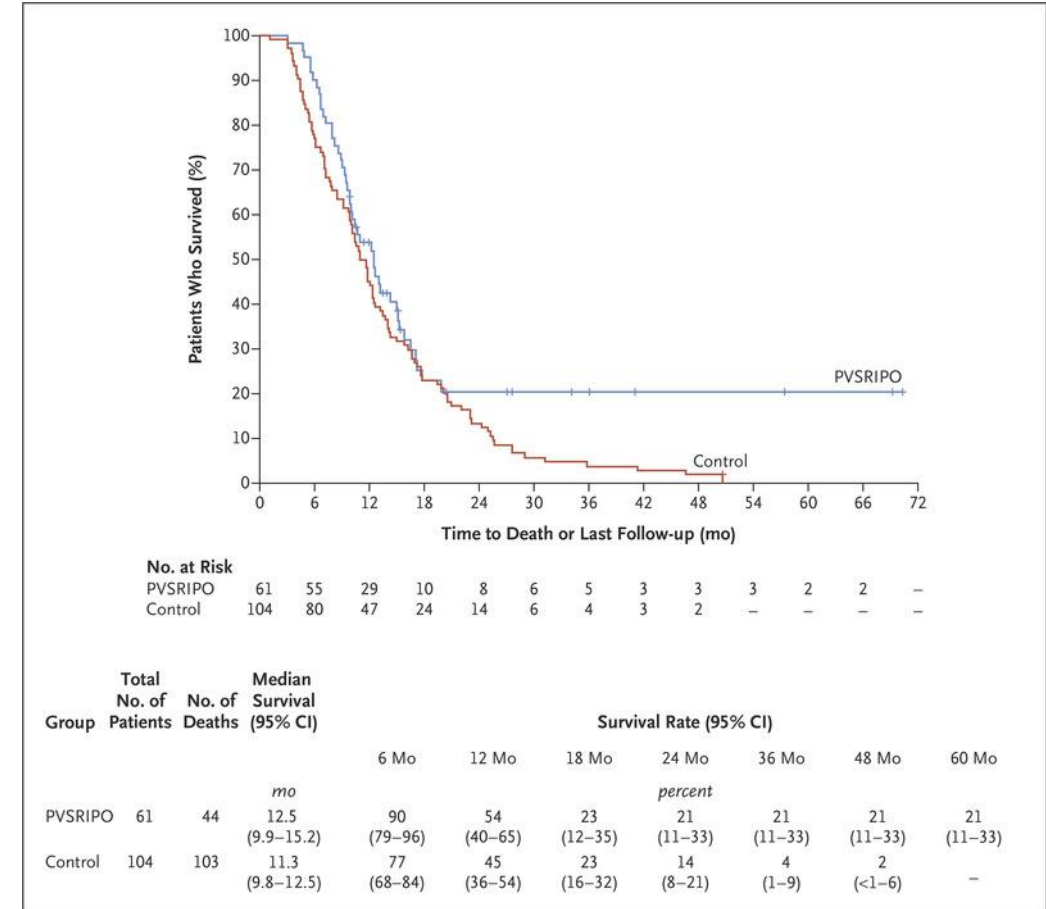


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Glioblastoma Treated with Recombinant Poliovirus

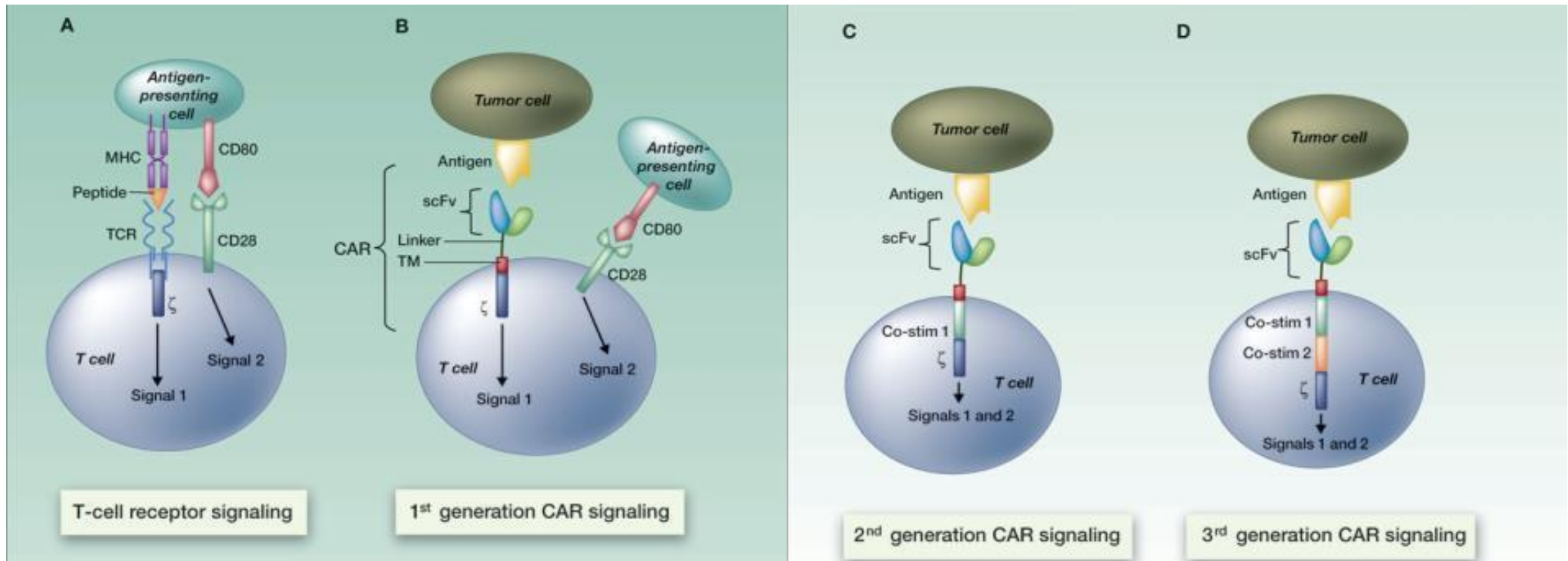
- PVSRIPO
 - Nonpathogenic polio-rhinovirus chimera
- Demographics
 - 61 pts with
 - Solitary 1 - 5.5 cm recurrence



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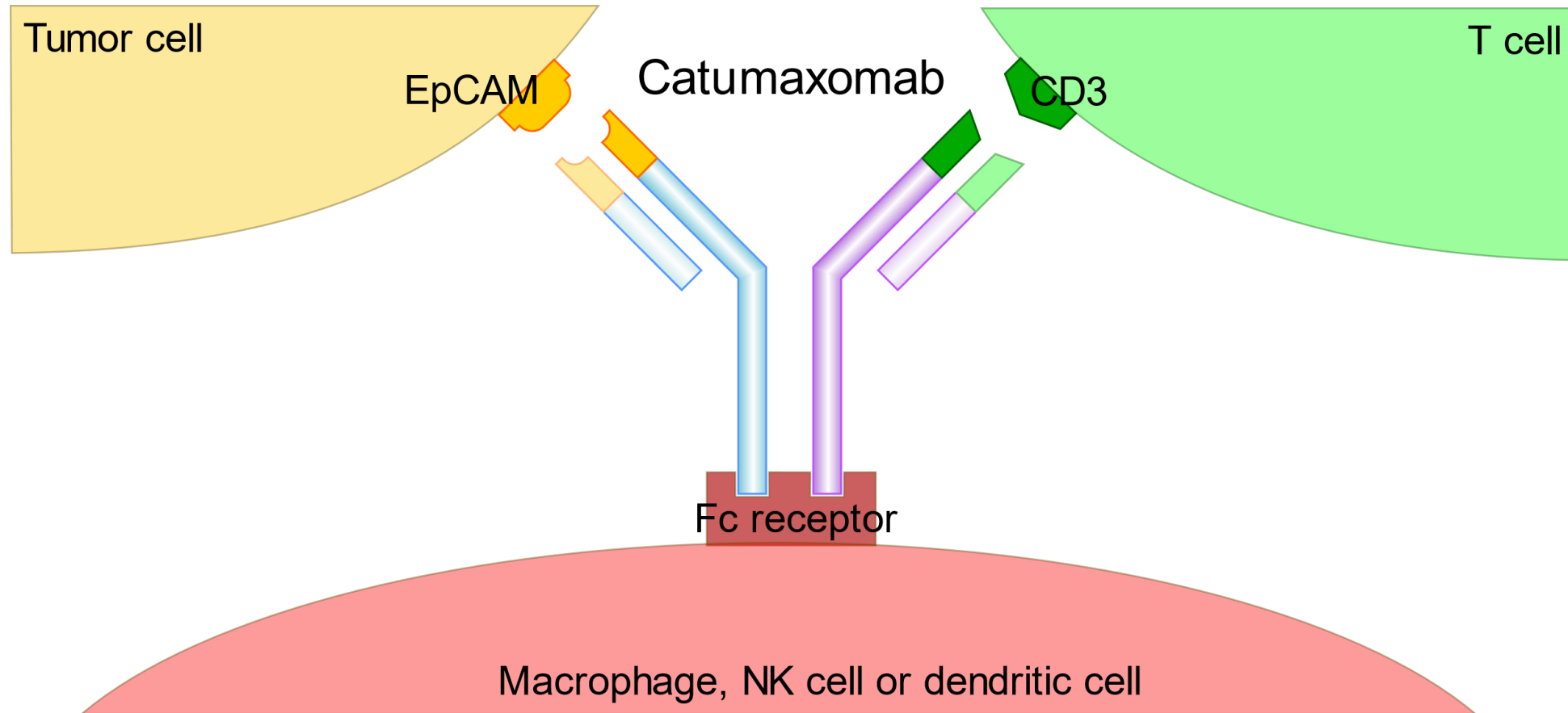
CAR-T Cells



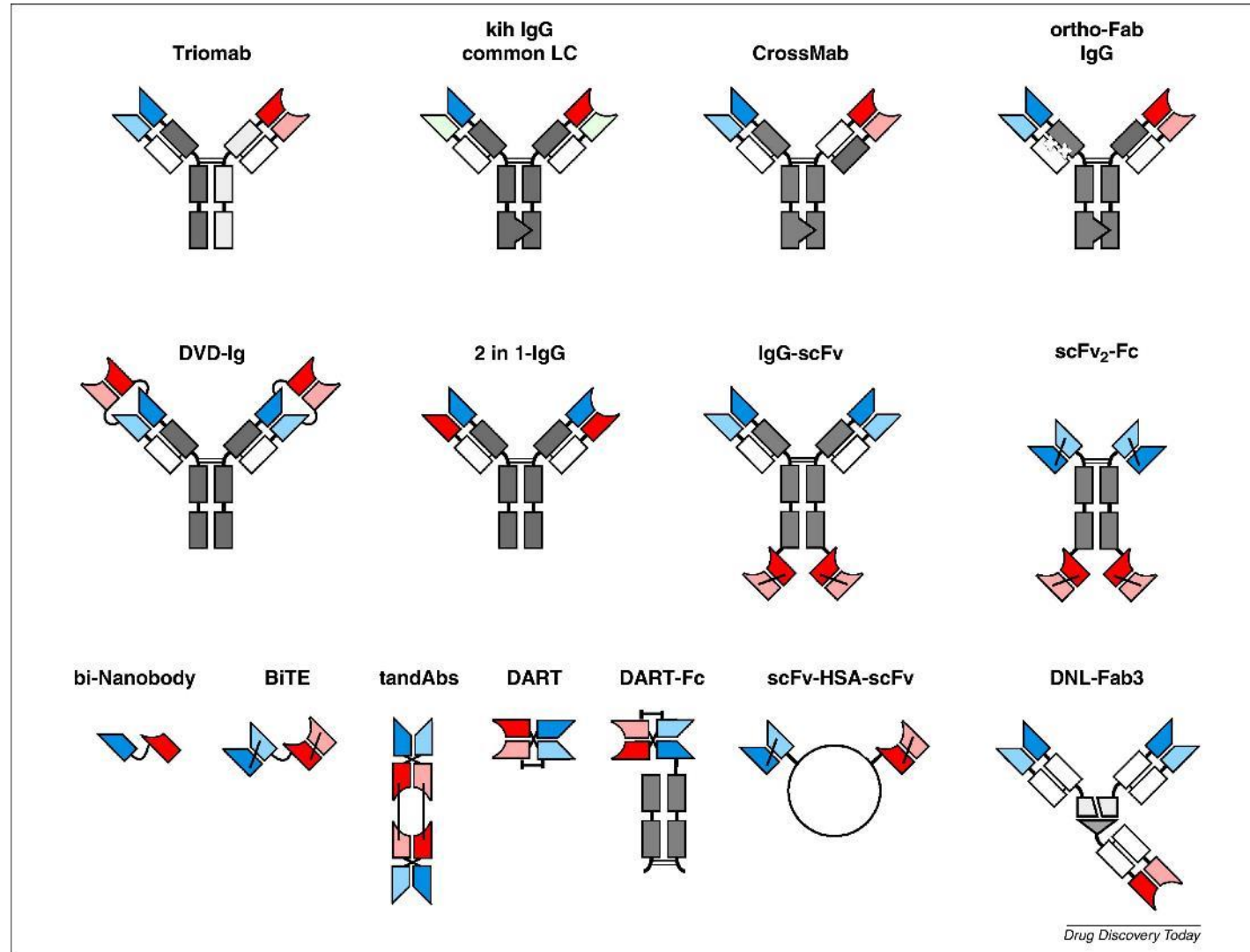
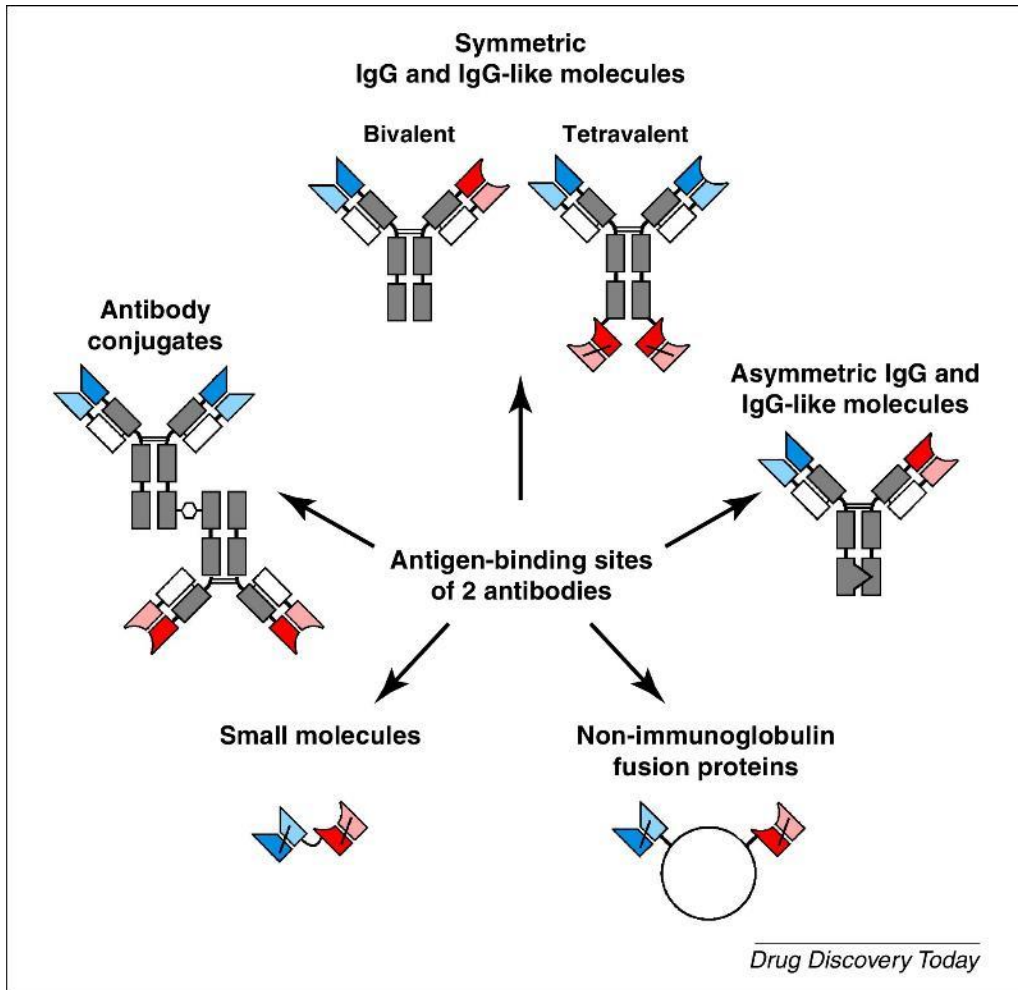
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Bispecific

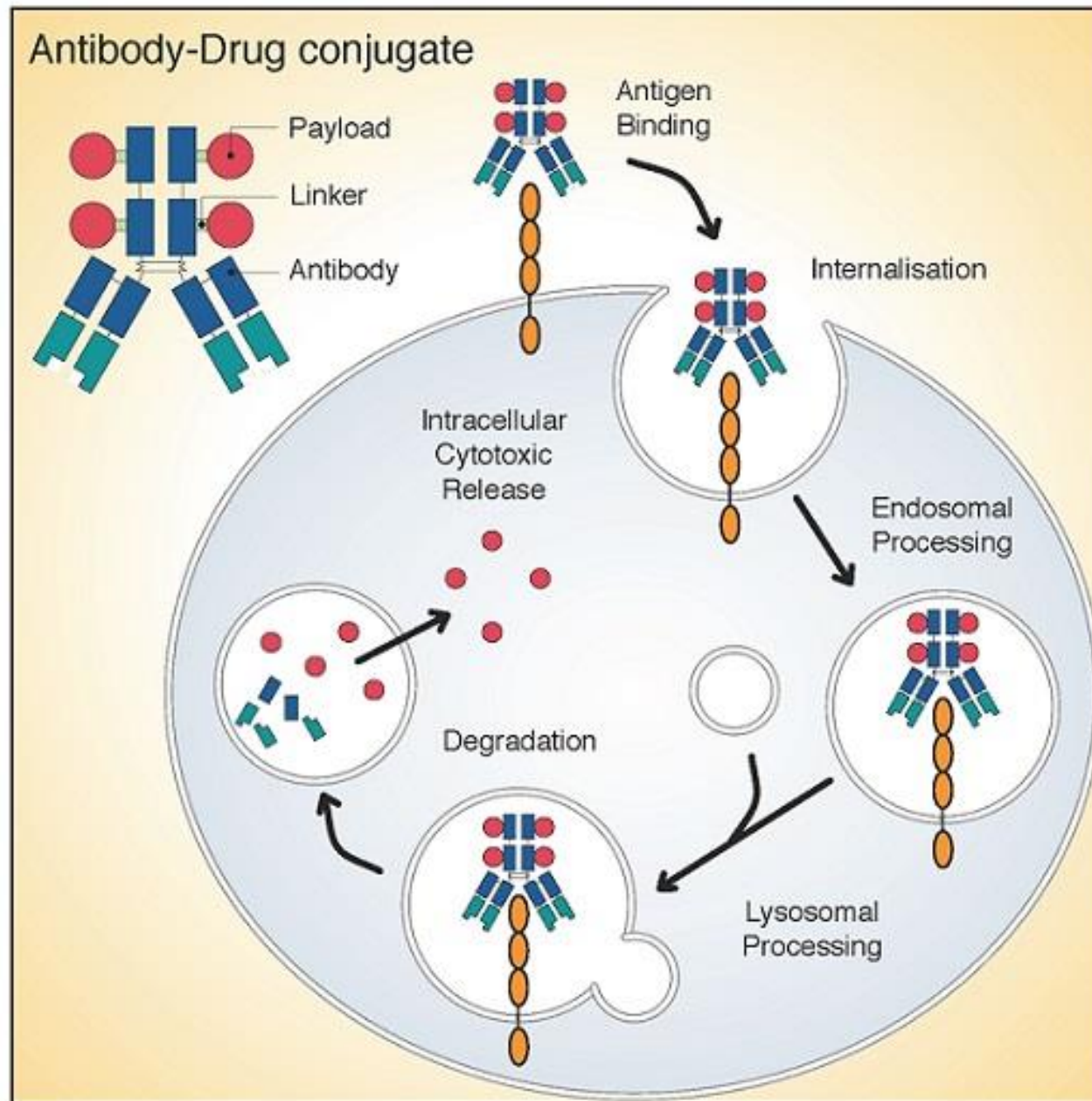


e.g. (CEA, PSMA, CD20, HER2, CD19) + CD3



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Combinations: e.g. GI Cancer

- Pancreas Cancer: PegPH20 + pembrolizumab
- Hepatocellular Cancer: Y90 + pembrolizumab
- Colon Cancer: Pembrolizumab +/- Mek Inhibitor +/- Chemotherapy
 - Atezolizumab + Cobimetinib in the 3rd line, press release negative.

Summary

- Anti PD1 + Anti CTLA4
- Anti PD1 + < Insert Your Anti Inhibitor >
- Anti PD1 + < Insert Your Agonist Stimulator >
- Anti PD1 + Chemotherapy
- Anti PD1 + Novel Agent to Make Immune System Work Better
- Oncolytic Viral Therapy
- Bispecific Antibodies
- CAR-T cells

