Immunotherapy of Cancer

OLLI, Fall 2020, Lecture 3

Ed Roy, Instructor

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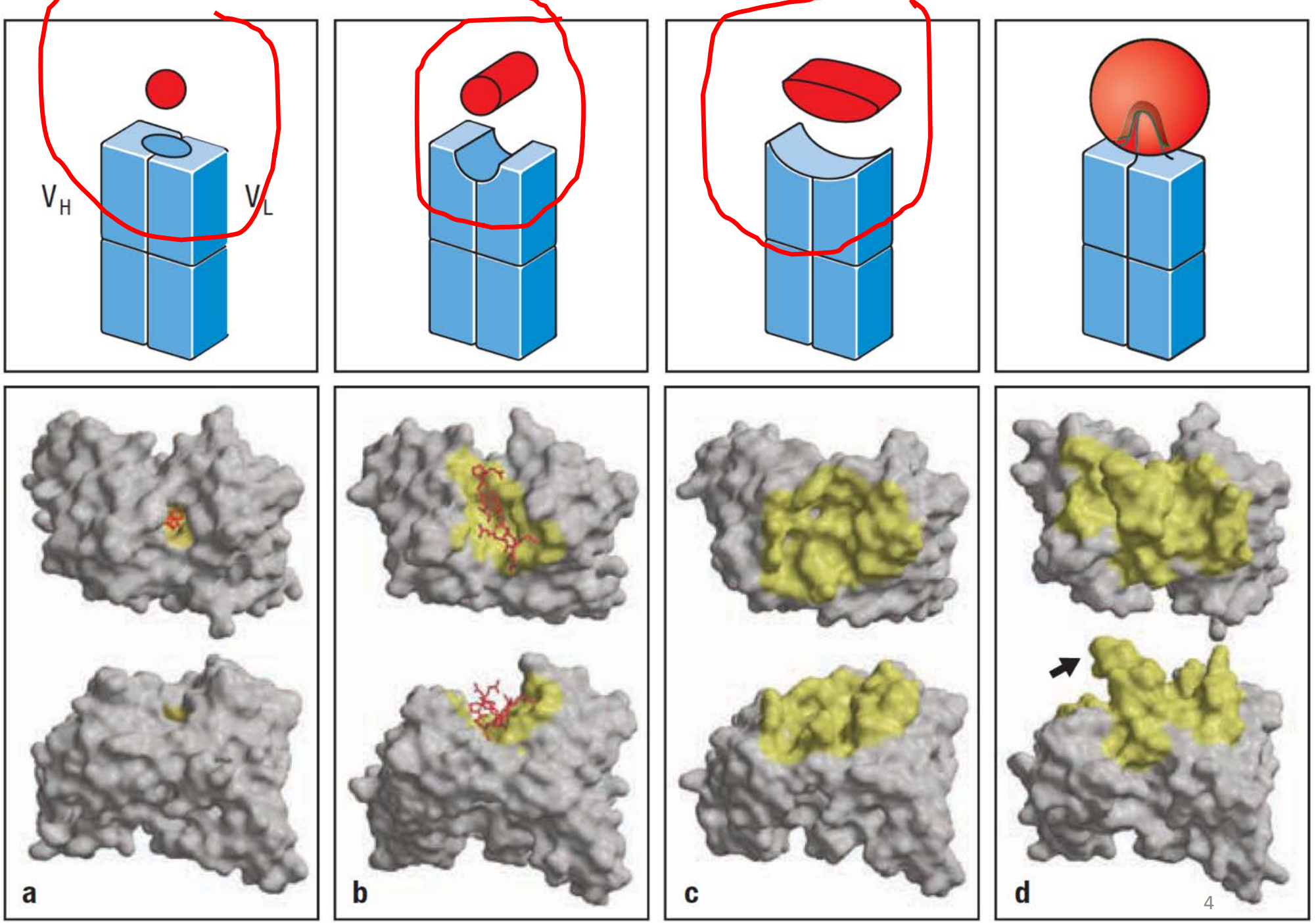
Reminder of OLLI Coffee

- Friday, October 23 – 9:00 a.m.
- We end the week – and the semester – where we began: with epidemiologist and OLLI instructor James Goodman Dobbins, who will talk about the ongoing developments in the fight against COVID-19 and the race to develop a vaccine. He will consider the following questions in this interactive session:
- - What COVID-19 vaccines are currently being developed for use in the U.S.?
- - Will these COVID-19 vaccines be safe and effective?
- - Should you be vaccinated against COVID-19?
- - If yes, then which vaccine should you select?

Quick Review from first lecture

- From Lecture 1, concept of recognition of antigen by antibodies and T cell receptors (TCRs), proteins binding to other molecules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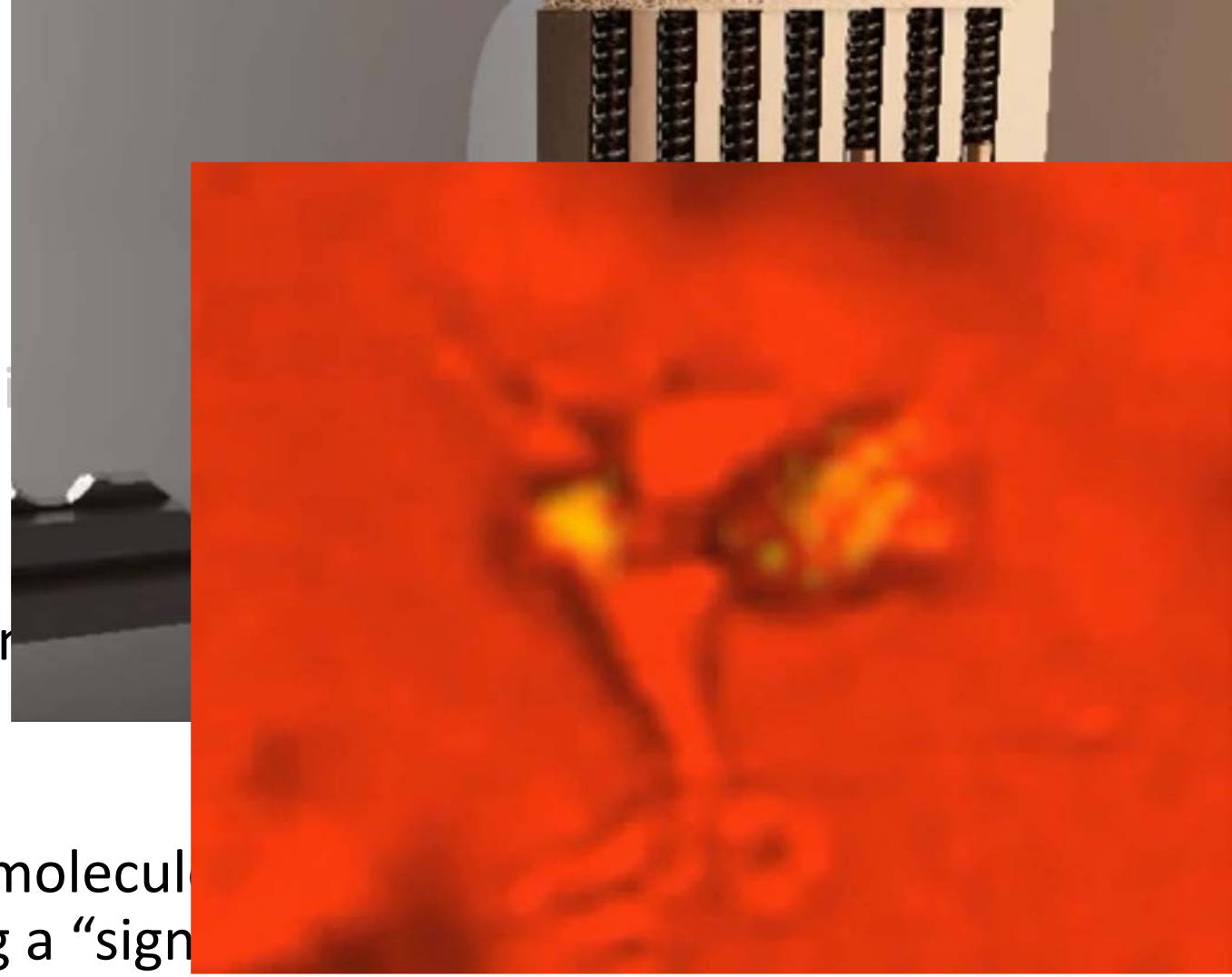
Quick Review



- From Lecture 1, concept of recogni
  receptors (TCRs)
- Proteins can bind other molecules
- The general term for such a protein
  - “B cell receptor” (antibody)
  - “T cell receptor”
- When receptors bind their target molecul
  change in the protein, propagating a “sign
- The signal changes the cell’s metabolism and function; this is described as “activation” of the B cell or T cell

More Review

- In Lecture 2, we also described how dendritic cells have “pattern recognition receptors” that bind to “pathogen associated molecular patterns” on pathogens (less specificity than antibodies and TCRs)
  - There are also “damage associated molecular patterns”
- Dendritic cells, part of the innate immune system, recognize “danger”, and then coordinate a response of the adaptive immune system (B cells and T cells)

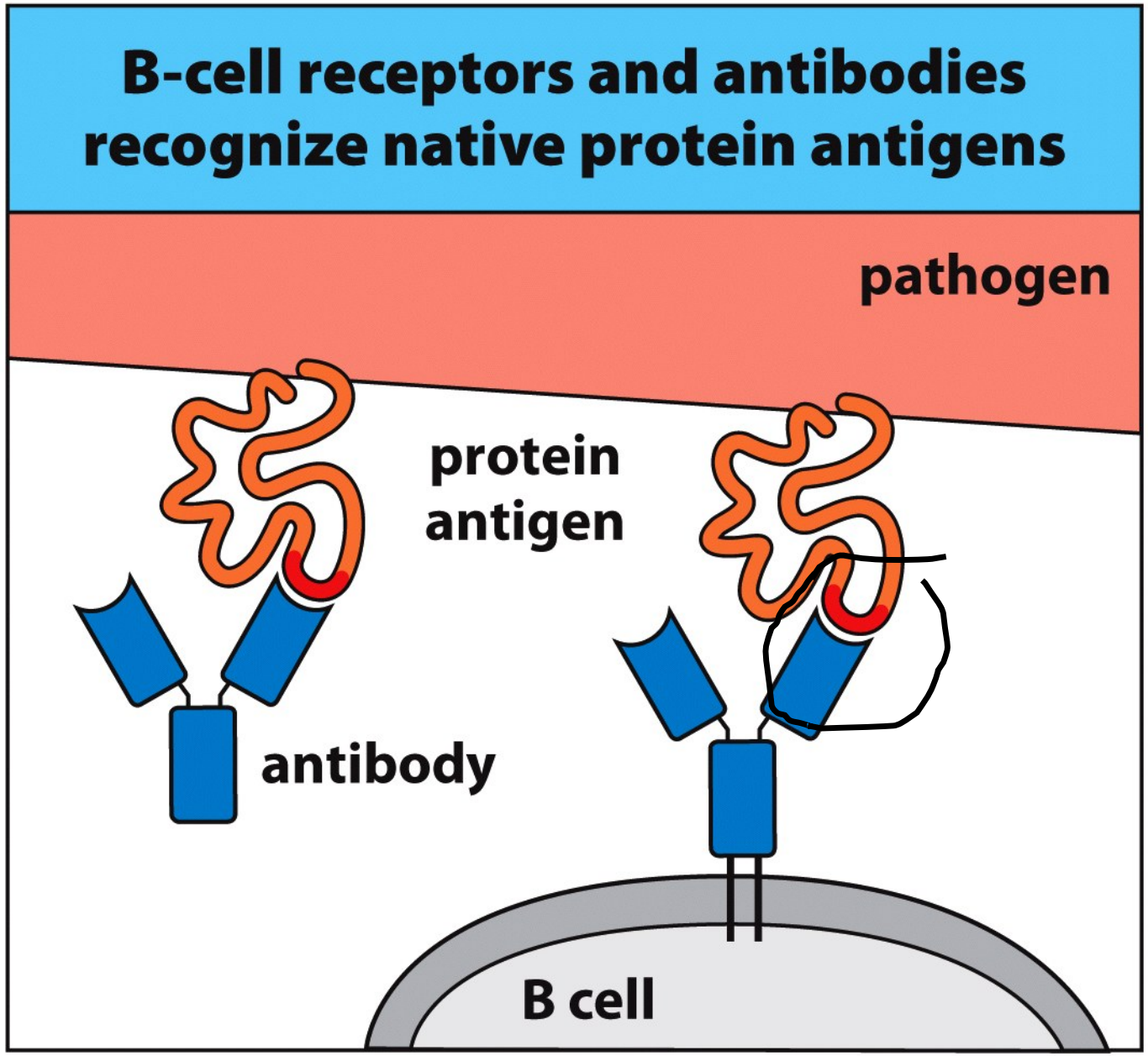
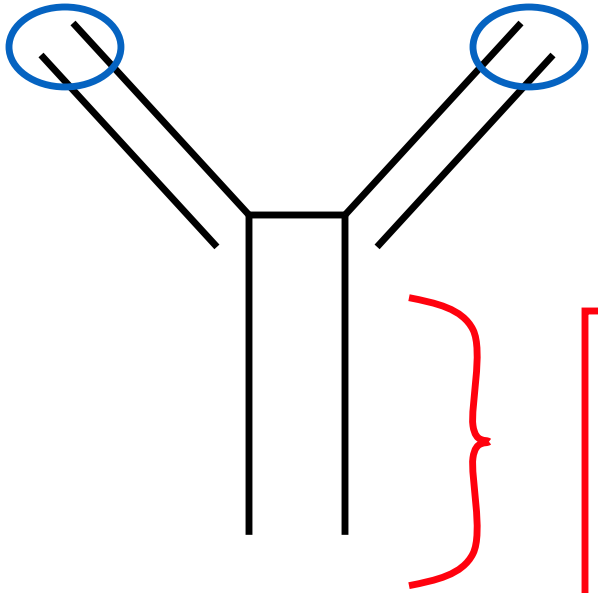


Figure 3.12 The Immune System, 3ed. (© Garland Science 2009)

Antibody Structure

Antigen Binding



Fc Region

Biological Activity (Effector Function)

Antibodies and TCRs are structurally similar

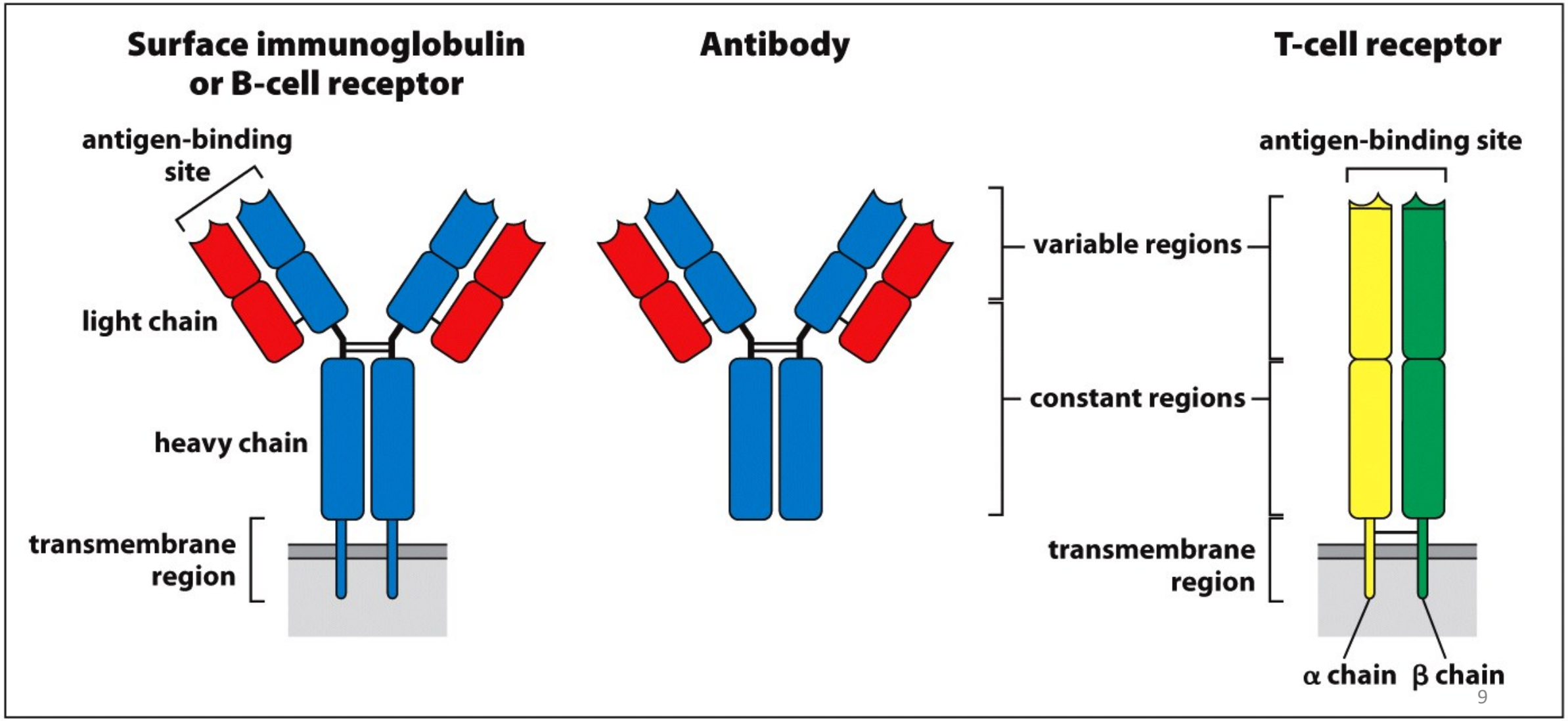


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

Negative Feedback on Immune Responses

- Regulatory T cells
- Brakes on T cells like CTLA-4 and PD-1

Lecture 3 Learning Objectives

- Learn about Cancer Mutations and Neoantigens
- Learn about Monoclonal Antibodies used to treat Cancer
- Learn about Cell Based Therapies for Cancer
  - T cells as Effectors
  - Cytokines to stimulate T cells
  - Checkpoint Inhibitors
  - Vaccines to enhance T cell activity
  - Adoptive Cell Therapies
  - CAR-T cell Therapies
  - Modification of Tumor Micro-Environment (TME) to reverse immunosuppression

Cancer Cells are Different from Normal Cells

- Genes have mutated in ways that allow them to proliferate and avoid the immune system
- Mutated genes encode mutated proteins; pieces of the mutated proteins potentially recognized by T cells are called **neoantigens**
- These mutated proteins are what immunotherapies target, in various ways
- Cell surface proteins can be targeted by antibodies
- Within-cell proteins can be targeted by T cells

Categories of Immunotherapy for Cancer

- Antibodies (Biologics)

- Cell based Therapies (mostly T cells)

Cell Based Therapies for Cancer

- Cytokines
- Checkpoint Inhibitors
- Vaccines including Dendritic Cell Vaccines
- BiSpecific T cell Engagers (BiTEs)
- Adoptive Transfer of T cells
  - Tumor Infiltrating Lymphocytes (TILs)
  - Engineered TCR T cells
  - Chimeric Antigen Receptor (CAR)-T cells
- Modification of Tumor Micro-Environment (TME) to reverse immunosuppression

Biologics: Antibodies

- Biologics are variations of naturally occurring proteins

Cancer Therapies

Traditional: Slash (Surgery), Burn (Radiation), Poison (Chemo)

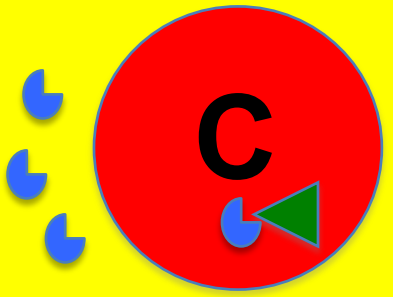
New Generation: Biologics and Immunotherapies

Class:	Chemo	Biologics	Cellular
	(small molecules)	(Large molecules called proteins)	(Whole cells)
Size:	~ 1 nanometer (nm)	10-100 nm	~10^4 - 10^5 nm
Delivery:	Oral	Intravenous (i.v.)	Intravenous (i.v.)
Examples:	Taxol, Vinblastin, etc	Antibodies like Herceptin	Patients own white blood cells (T cells)
Companies:	Most Big Pharma, e.g. Merck, AbbVie	All big Pharma/ some Biotech, e.g. Genentech, Amgen	Novartis, Juno, Kite, Adaptimmune, a few others

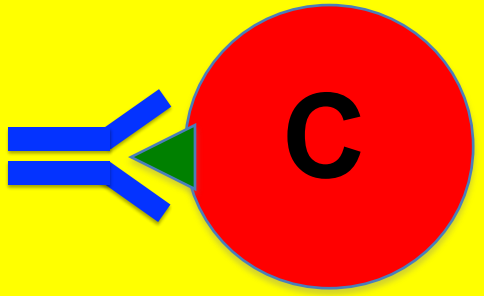
Kranz,

Targeted Cancer Therapies

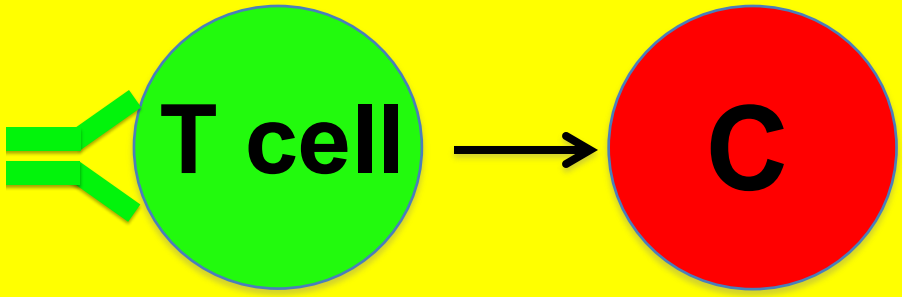
Identification of Cancer Targets Inside the Cell



Identification of Cancer Targets on Surface

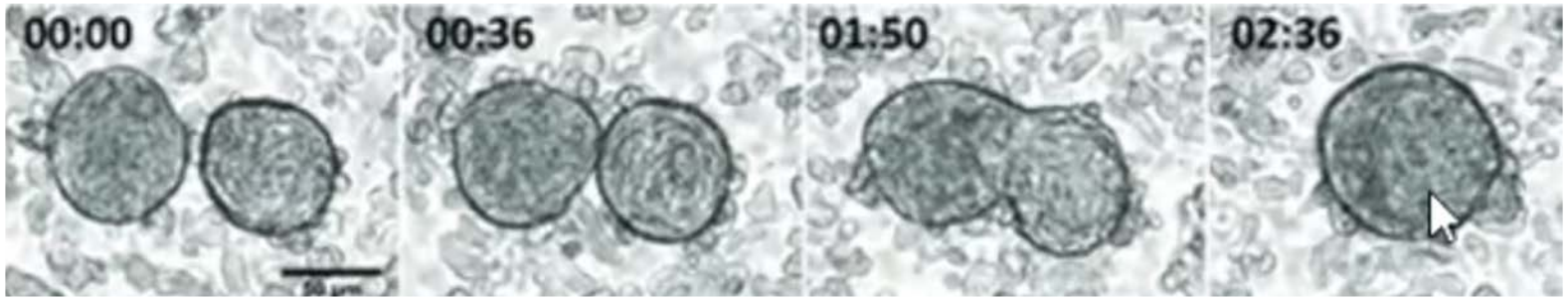


Activate Immune Cells to Kill Cancer Cells



What is a Monoclonal Antibody?

- Derived from a single B cell, so it is monoclonal
- B cell is fused with a myeloma cell to immortalize it
- These “hybridoma cells” pump out antibody molecules, all identical



Uses of Manufactured Monoclonal Antibodies for Cancer Treatment

1. Direct Killing of Cancer Cells
2. Interference with Signaling Receptors Required by Cancer Cells
3. Delivery of other agents that kill Cancer Cells (poisons, radiation)
4. Disruption of blood supply to cancer cells by targeting VEGF
5. Enhancement of Cellular T cell responses
    1. Modulation of T cell responses
    2. Linkage of Cancer Cells to activation of T cells

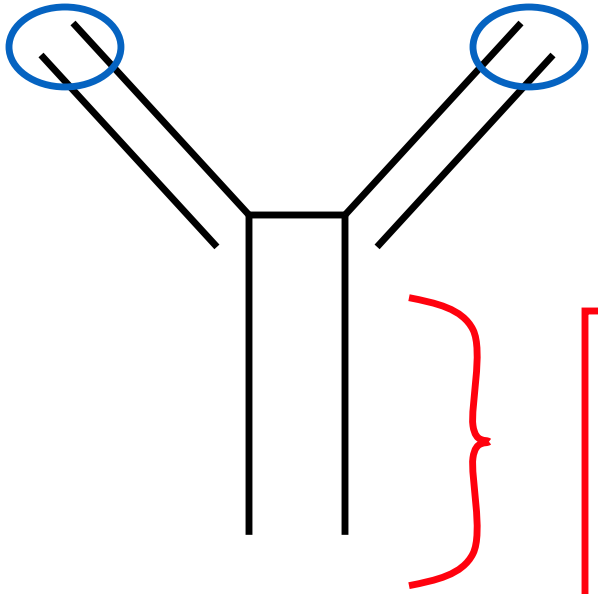
How does an antibody directly kill cancer cells?

- “Effector mechanisms” largely determined by constant region of antibody, the Fc region

Antibody Structure

Antigen

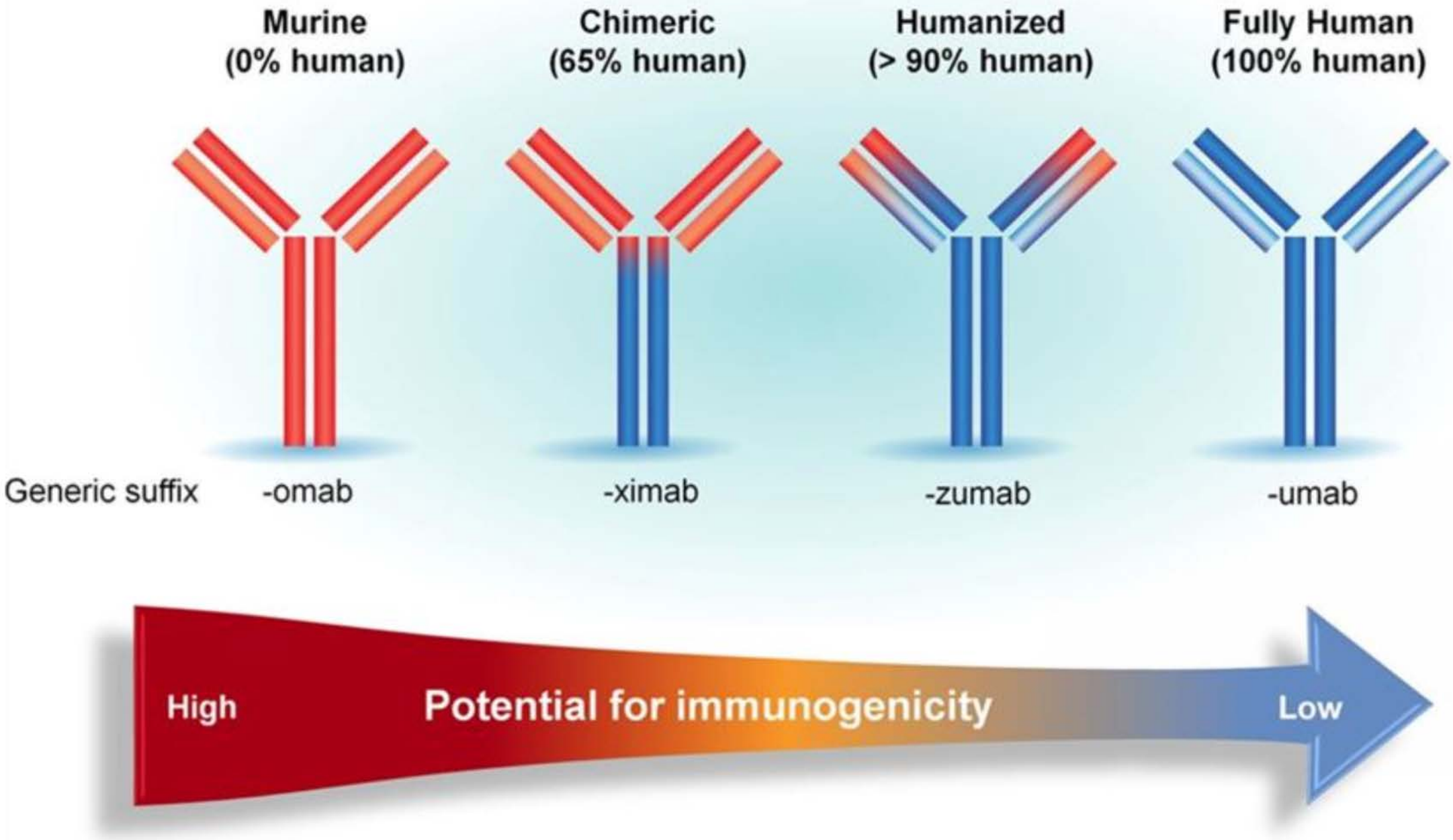
Binding



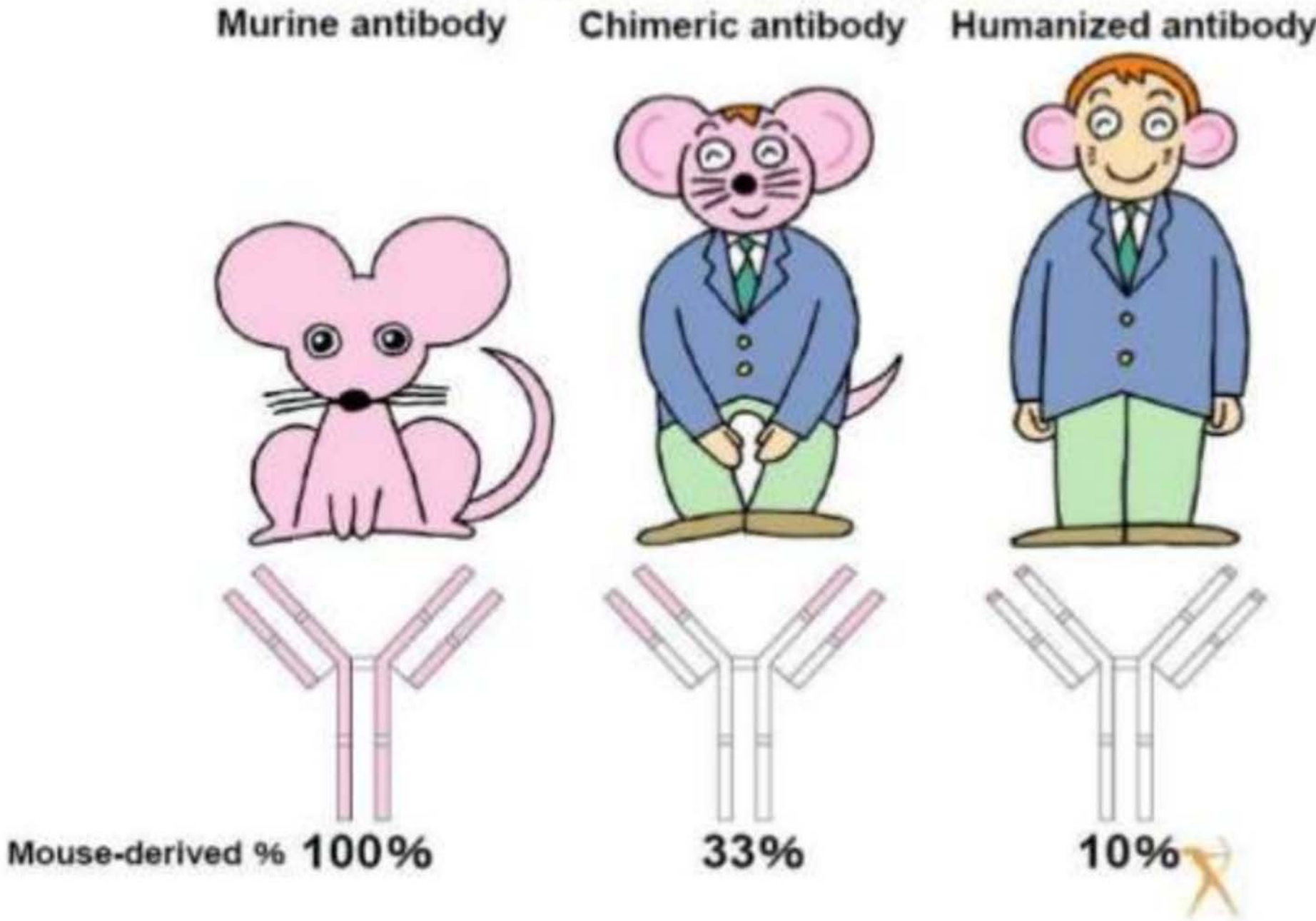
Fc Region

Biological Activity
(Effector Function)

- 1980 first mouse monoclonal antibody used to treat cancer, but Human Anti-Mouse Antibodies (HAMA) formed
- Humanized antibodies in 1988


Murine
(0% human)
Chimeric
(65% human)
Humanized
(> 90% human)
Fully Human
(100% human)
Generic suffix
-omab
-ximab
-zumab
-umab
High
Potential for immunogenicity
Low

Differences in antibodies



Khawaja, share

Terminology

- Decoder at https://en.wikipedia.org/wiki/Nomenclature_of_monoclonal_antibodies

- rituximab (Rituxan)
- Ipilumumab (Keytruda)

- “Biosimilars” are analogous to generics for small molecules, after patent expires

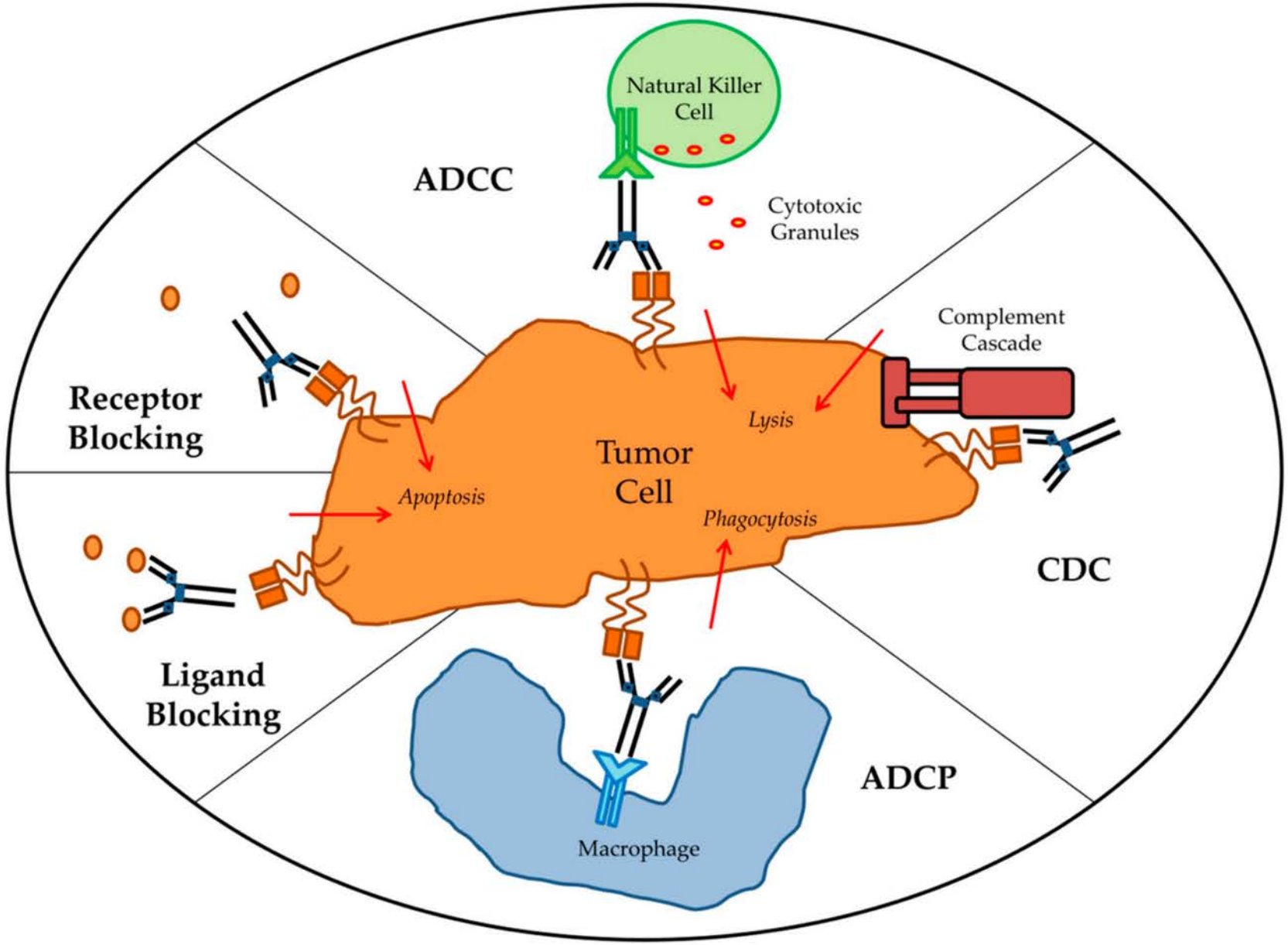


Figure 1. Antibody effector mechanisms. ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity; ADCP: antibody-dependent cellular phagocytosis.

Zahavi and Weiner, 2020

Monoclonal Antibodies in Cancer Therapy

Clinical Uses

Direct Tumor Targeted
Antibody-Drug Conjugates
Microenvironment Targeted
BiTEs
Immune Checkpoint Inhibitors

Effector Mechanisms of Targeted mAbs

Receptor Blocking
Ligand Blocking
ADCC
CDC
ADCP

Mechanisms of Resistance

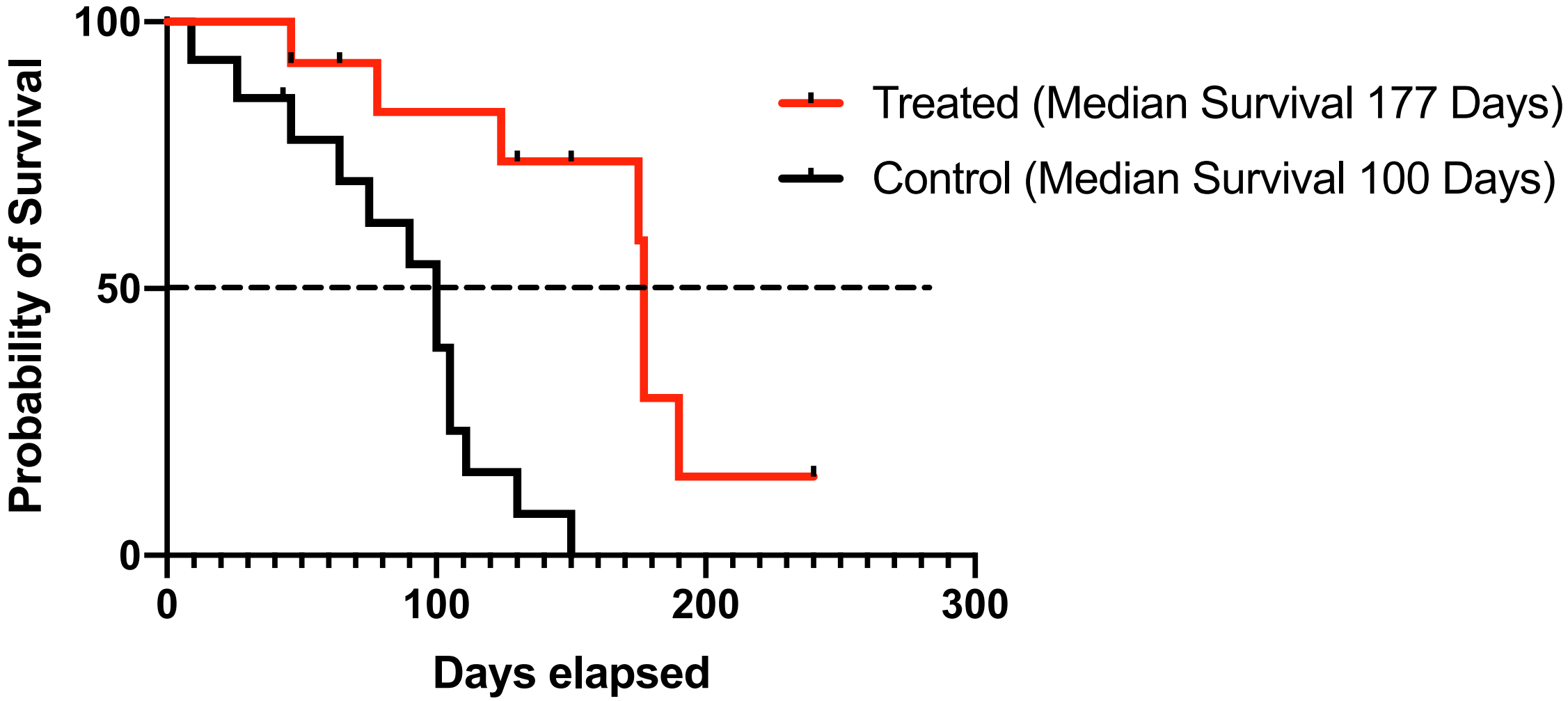
Mutations or Loss of Antibody Target
Alternative Growth/Survival Signaling
Epithelial to Mesenchymal Transition
Impaired Effector Cell Responses

Zahavi and Weiner, 2020

Metrics for Evaluating a treatment

- Objective Response Rate (ORR) – % some shrinkage of tumor size
- Complete Response (no evidence of tumor)
- Progression Free Survival (PFS) or Time to Progression
- Overall Survival (OS): Median Survival Time

Clinical Trial of New Cancer Treatment



Targets on cancer cells

- EGFR – epidermal growth factor receptor
  - Common in colorectal cancer
  - Cetuximab (Erbitux)(2 months median survival increase)

- HER2 – human epidermal growth factor receptor 2
  - Common on breast cancer
  - Trastuzumab (Herceptin)(8 months median survival increase, cardiotoxicity)

- CD20
  - on non-Hodgkin lymphoma and normal B cells
  - Rituximab (Rituxan) first mAb in 1988 (6-12 month Progression-free Survival)

Monoclonal antibodies also used to deliver toxins, radiation, etc.

Cell Based Therapies

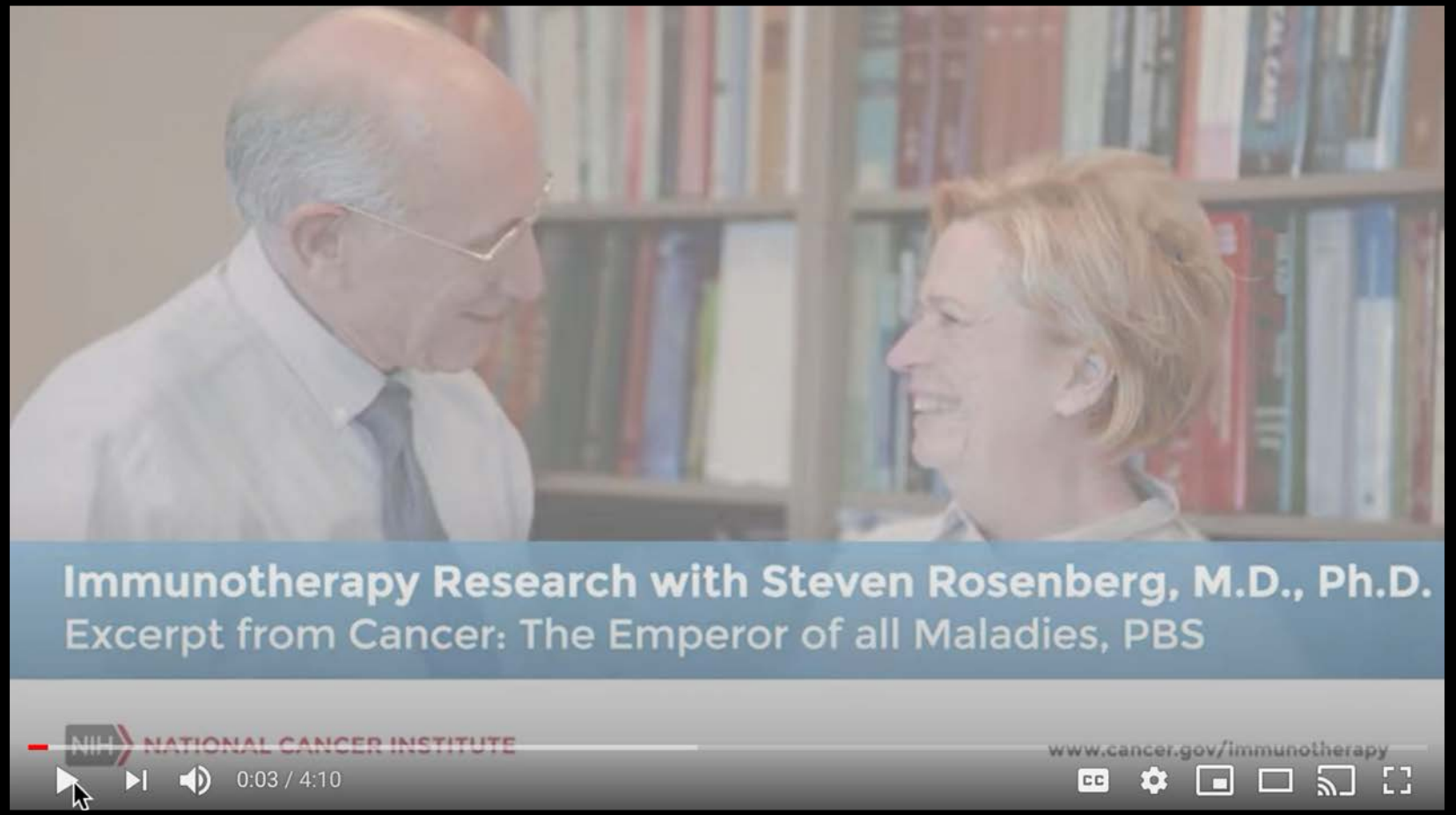
- Try to direct T cells to kill cancer cells
- Each T cell can kill many cancer cells
- T cell receptor can recognize tumor peptide presented on MHC on the surface of tumor cell (the mutated protein does not have to be a membrane protein)

Pioneers of T cell Therapies: Phil Greenberg, Steven Rosenberg, Jim Allison (2011 photo)

Steven Rosenberg

- Head of Surgery Branch at National Cancer Institute
- Very aggressive in trying things in patients
- 2014 article describes IL-2 as first successful immunotherapy for cancer, first patient success treated in 1984
- 20-30% response rate
- 1% died from treatment

Dr. Steven Rosenberg and patient in 1984. Photo courtesy of NCI


Immunotherapy Research with Steven Rosenberg, M.D., Ph.D.
Excerpt from Cancer: The Emperor of all Maladies, PBS
NIH NATIONAL CANCER INSTITUTE
www.cancer.gov/immunotherapy
0:03 / 4:10

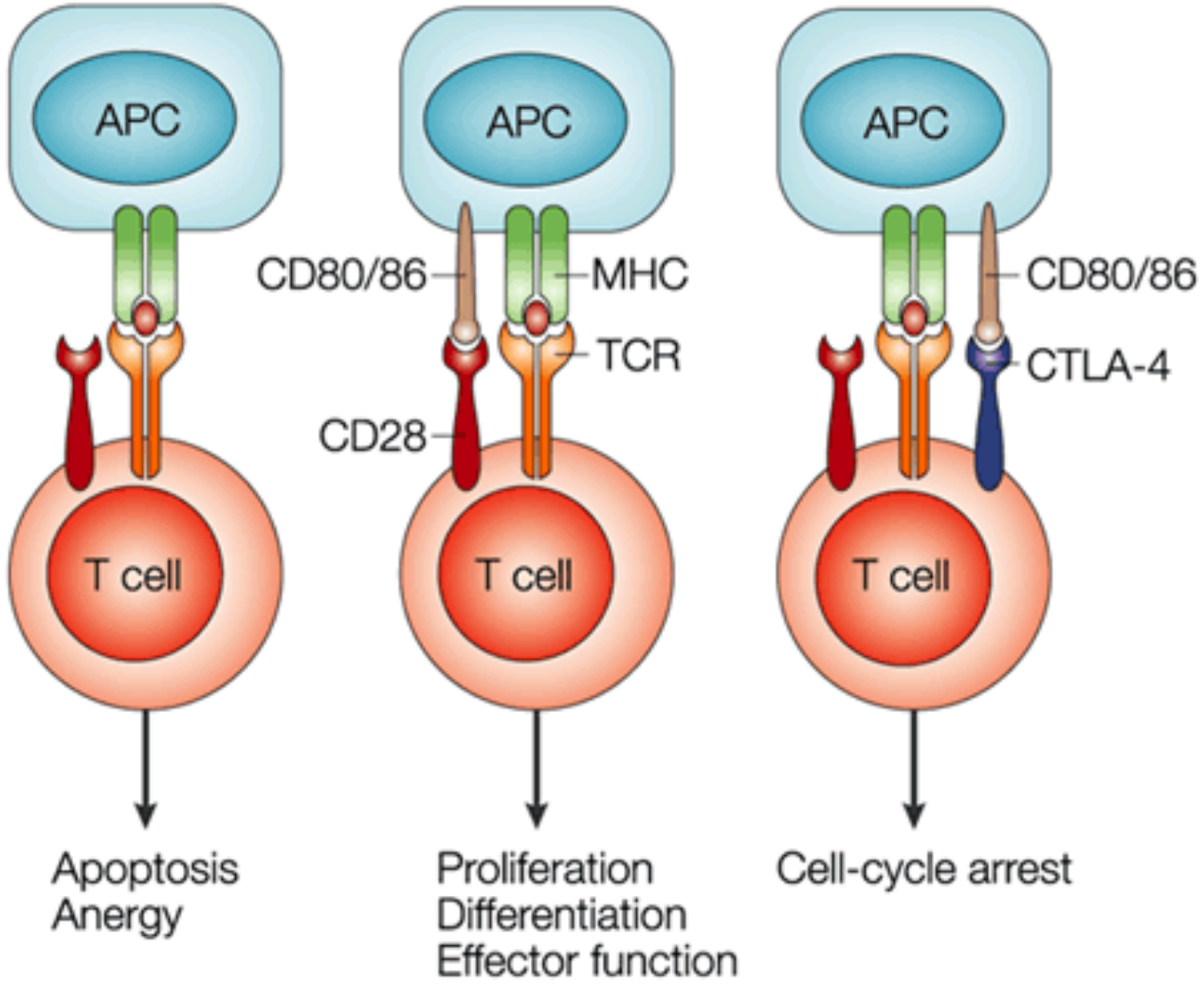
Cytokines as Therapy

- Discovery of IL-2 in 1976 allows T cells to remain alive and proliferate in tissue culture
- Has been used as therapy for metastatic melanoma and kidney cancer
- IL-2’s ability to sustain T cells in culture allowed development of adoptive T cell therapy approaches
- Rosenberg also contributed adoptive T cell therapies, which we will cover later

Checkpoint Inhibitors

- CTLA-4 and PD-1 are “brakes” or “checkpoints” on T cells, that shut off an ongoing T cell response

Activation sets in motion multiple mechanisms to end the response, e.g. CTLA-4 and PD-1 on T cells



CD28 and CTLA-4 Have Opposing Effects on the Response of T cells to Stimulation

By Matthew F. Krummel and James P. Allison

From the Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, California 94720

Summary

The importance of the B7/CD28/CTLA-4 molecules has been established in studies of antigen-presenting cell–derived B7 and its interaction with the T cell costimulatory molecule CD28. CTLA-4, a T cell surface glycoprotein that is related to CD28, can also interact with B7-1 and B7-2. However, less is known about the function of CTLA-4, which is expressed at highest levels after activation. We have generated an antibody to CTLA-4 to investigate the consequences of engagement of this molecule in a carefully defined system using highly purified T cells. We show here that the presence of low levels of B7-2 on freshly explanted T cells can partially inhibit T cell proliferation, and this inhibition is mediated by interactions with CTLA-4. Cross-linking of CTLA-4 together with the TCR and CD28 strongly inhibits proliferation and IL-2 secretion by T cells. Finally, results show that CD28 and CTLA-4 deliver opposing signals that appear to be integrated by the T cell in determining the response to activation. These data strongly suggest that the outcome of T cell antigen receptor stimulation is regulated by CD28 costimulatory signals, as well as inhibitory signals derived from CTLA-4.

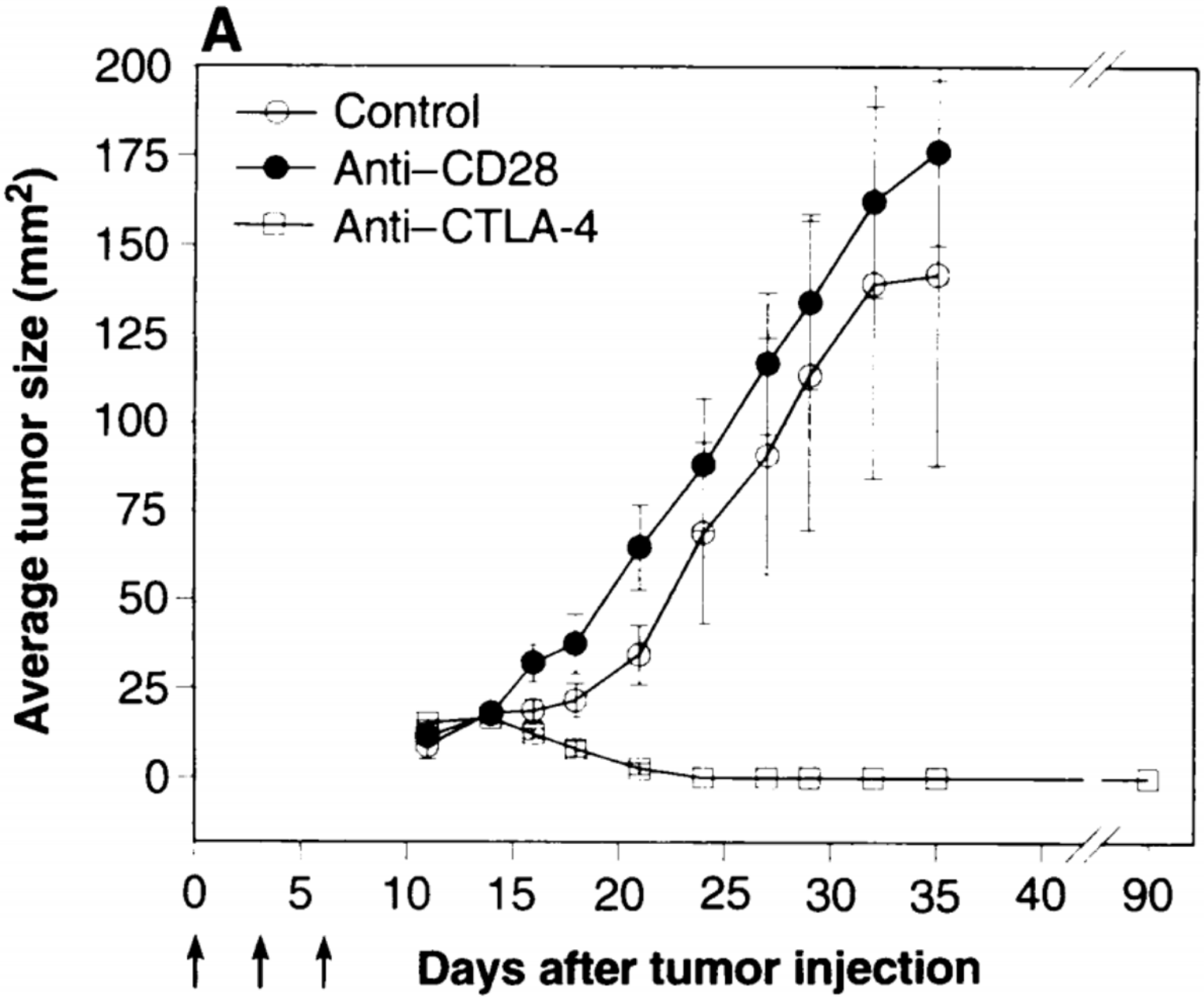
JEM, 1995

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison*

One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

Science, 1996 March


A
Control
Anti–CD28
Anti–CTLA-4
Average tumor size (mm²)
200
175
150
125
100
75
50
25
0
0
5
10
15
20
25
30
35
40
90
Days after tumor injection

Jim Allison Independent Lens PBS

- https://www.pbs.org/video/jim-allison-breakthrough-vriyqn/

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Time from Initial Publication to First in Class FDA Approval

	Initial Paper	FDA
Monoclonal Antibodies to Cancer Surface Targets	1975	1997
Antibody Drug Conjugates (ADCs)	1975	2000
Monoclonal Antibodies to Angiogenesis Targets	1993	2004
Checkpoint Inhibitors (Antibodies to T Cells)	1996	2011
Bispecific T Cell Engagers (BiTEs)	1985	2014
Chimeric Antigen Receptor T Cells (CAR)	1989	2017

Time from Initial Publication to First in Class FDA Approval

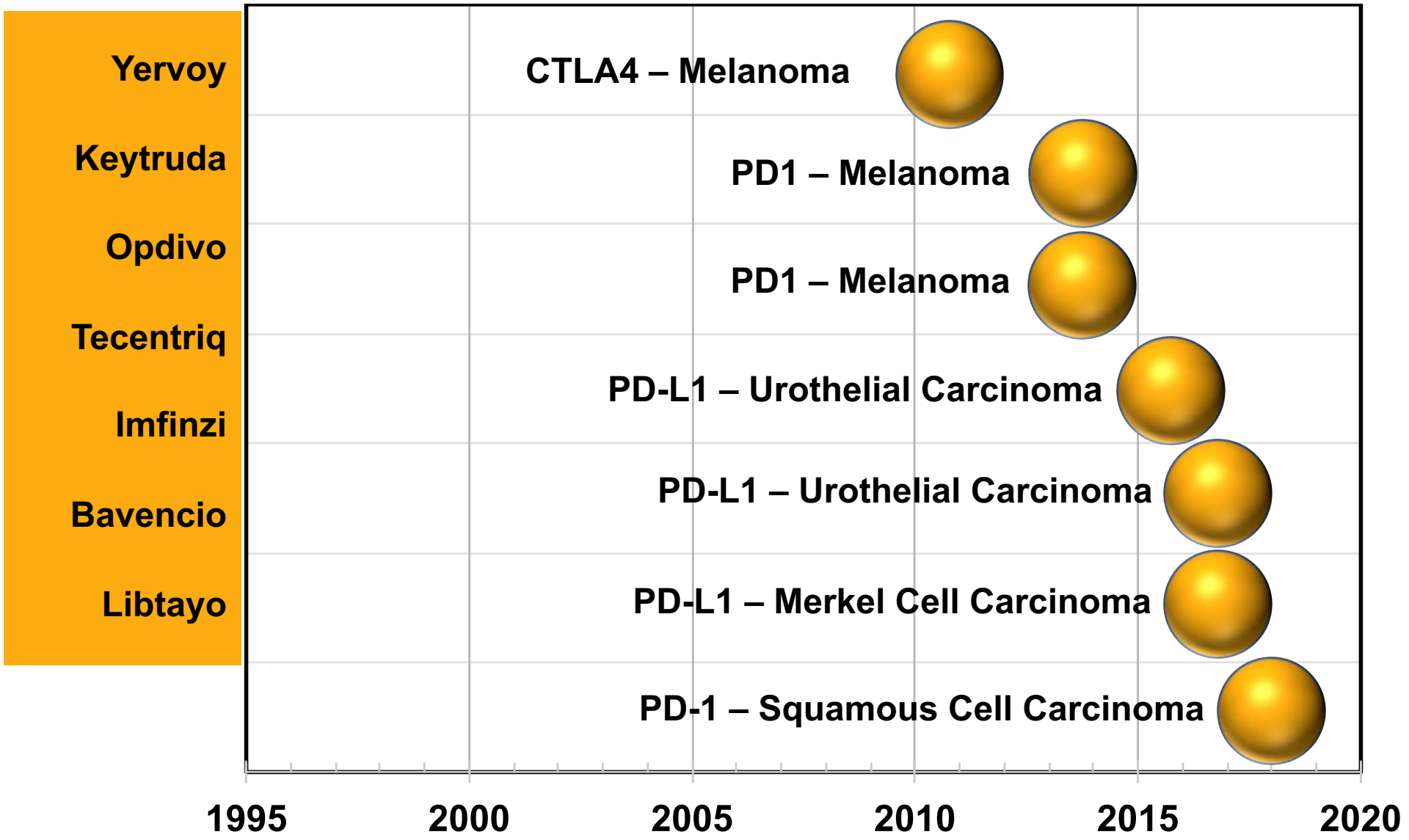
Monoclonal Antibodies to Cancer Surface Targets	1975 ➔ 1997
Antibody Drug Conjugates (ADCs)	1975 ➔ 2000

Ave = 21.6 years

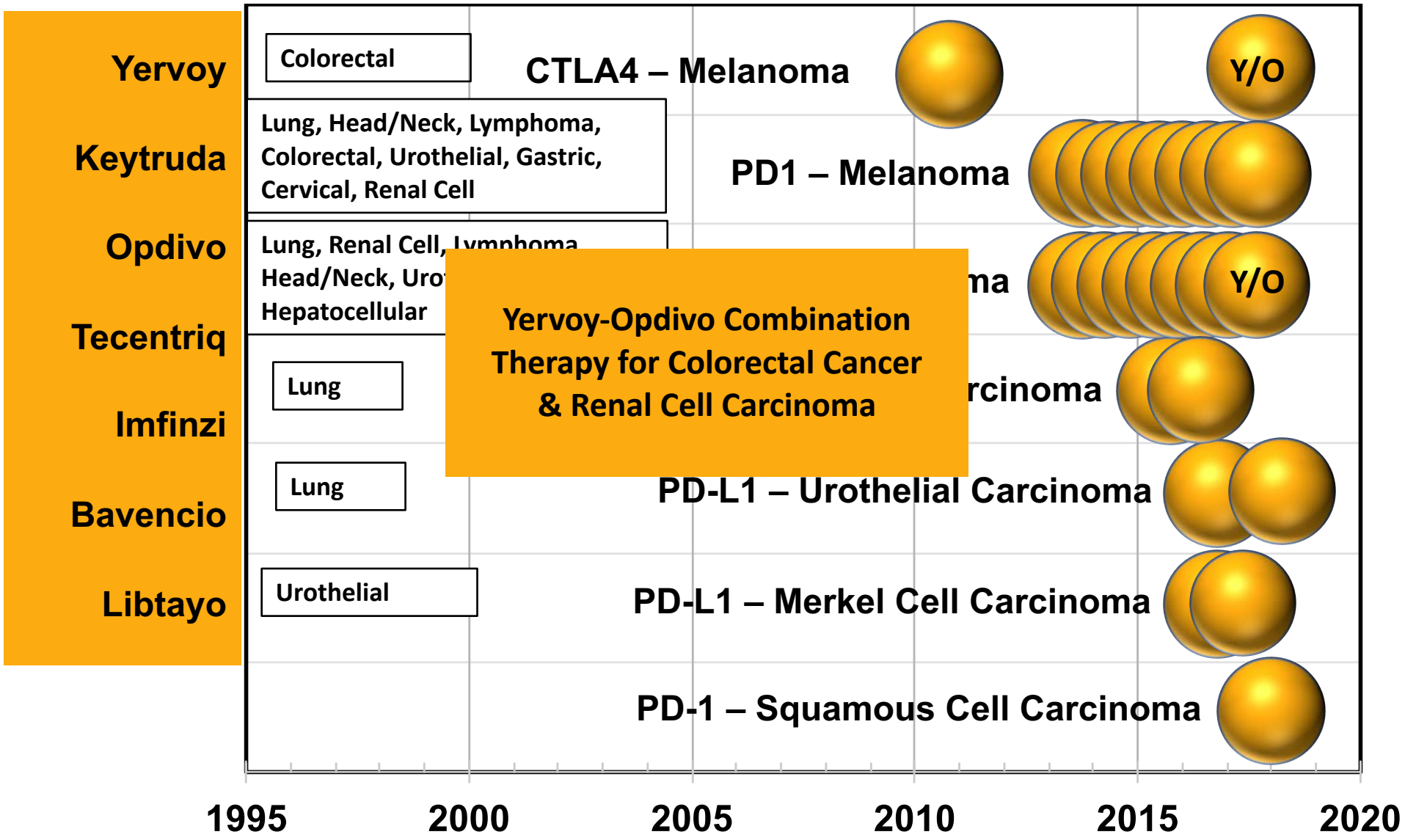
Range, 11 – 29 years

Patent Lifetime = 20 years

Immune Checkpoint Inhibitors

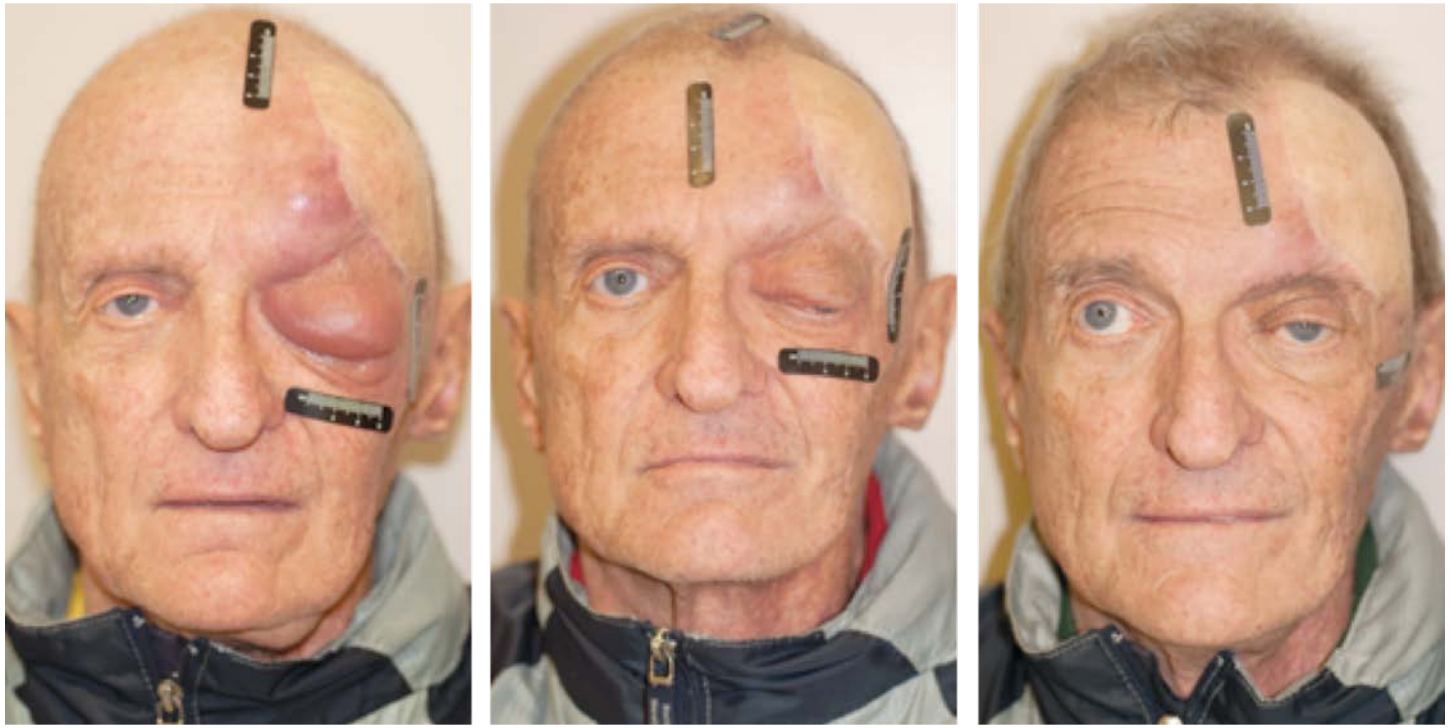


Immune Checkpoint Inhibitors



Anti-PD-1 Monoclonal Antibody Therapy

From *OncoLog*, February 2014, Vol. 59, No. 2
From MD Anderson Cancer Center

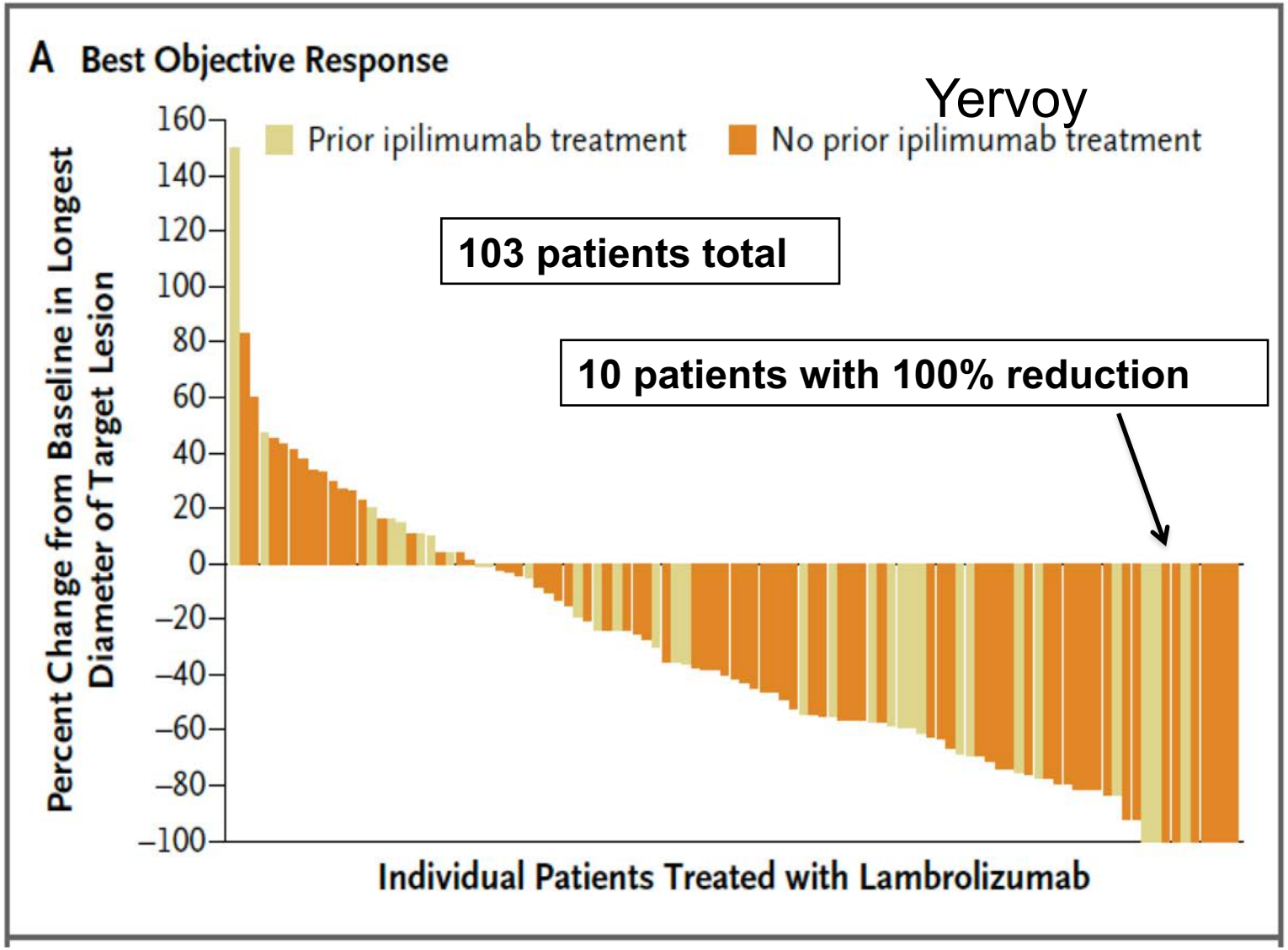


A patient with melanoma is shown before (left), after one cycle, and after three cycles of treatment with the anti–PD-1 antibody MK-3475 (10 mg/kg every 3 weeks)

SCIENCE Magazine Breakthrough of 2013

Seek and destroy. Instead of targeting tumors directly, cancer immunotherapy enlists the immune system to attack them. Here, an antibody (pink) blocks a receptor (blue) found on T cells (gray), setting off a chain reaction that leads to an assault on cancer cells.

Efficacy: Immune Checkpoint Inhibitor Keytruda in Melanoma Patients



Hamid et al, 2013, N Eng J Med, 369:2

The Nobel Prize in Physiology or Medicine 2018

Cancer therapy: Releasing the brakes of immunity

The Nobel Prize in Physiology or Medicine 2018 was awarded to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation." The Laureates has shown how different strategies for inhibiting the brakes on the immune system can be used in the treatment of cancer. Their discoveries are a landmark in our fight against cancer.

© The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén

Combination of Two Checkpoint Inhibitors works even better

- Anti-CTLA-4 and Anti-PD-1

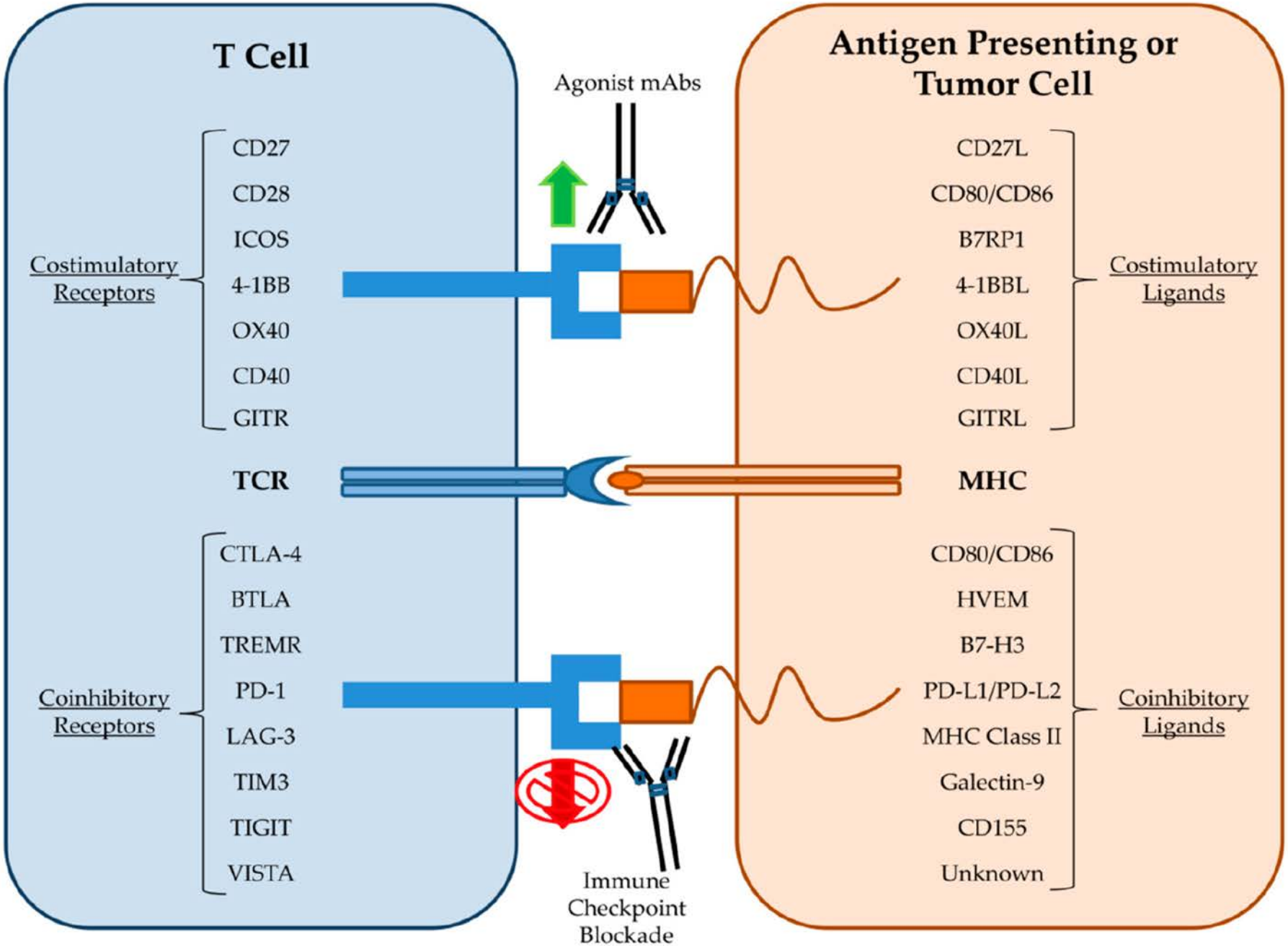
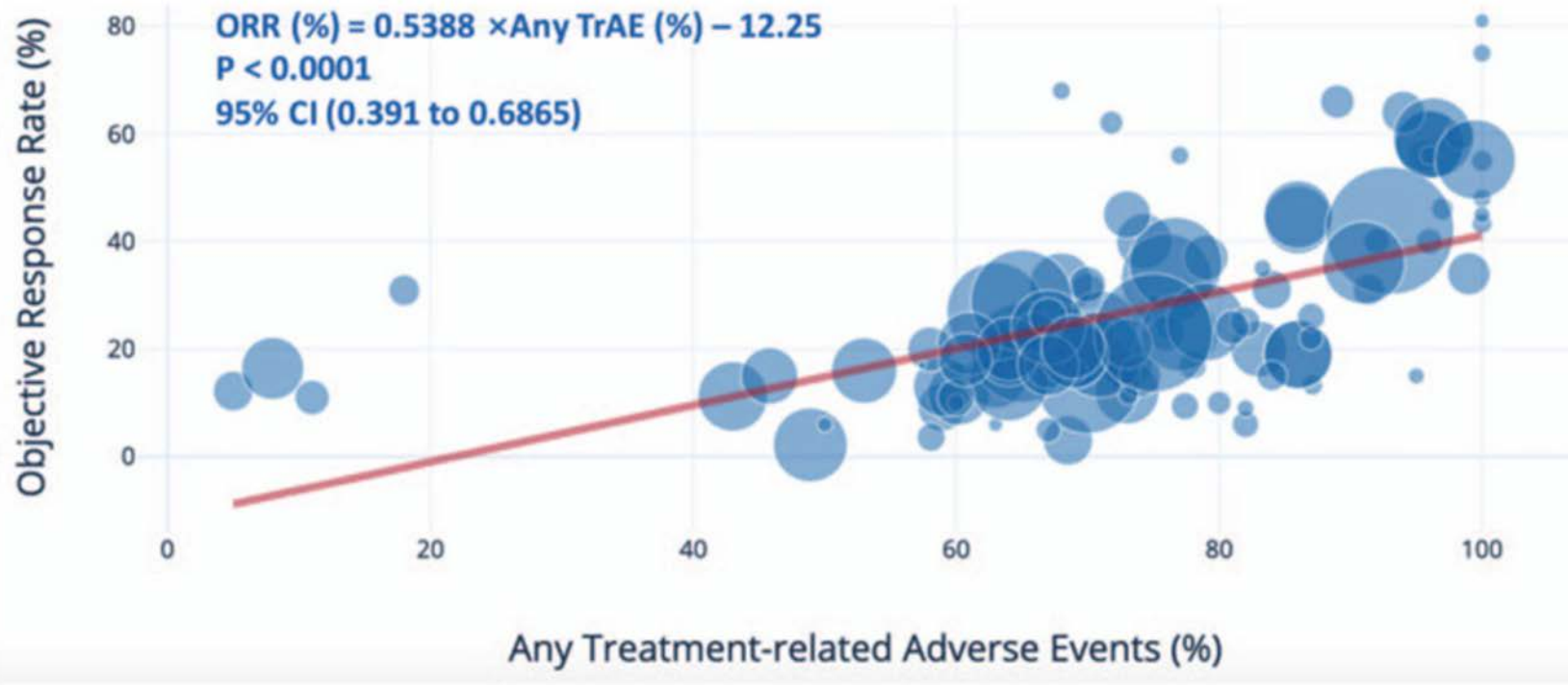
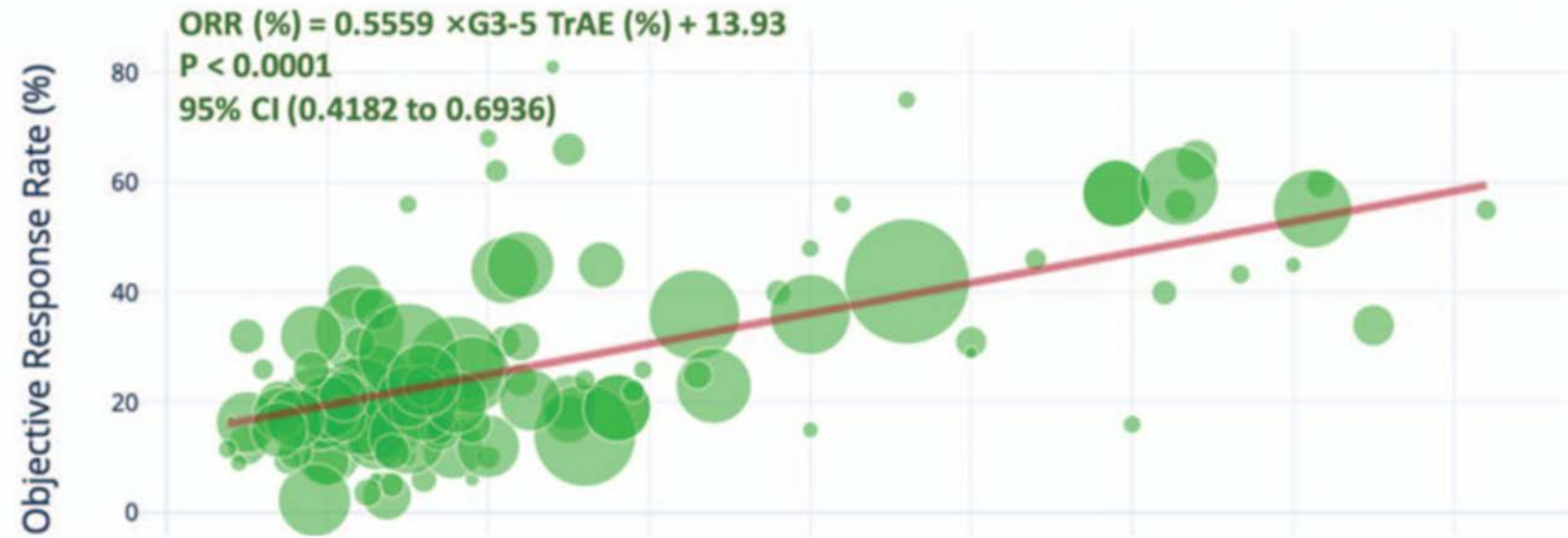


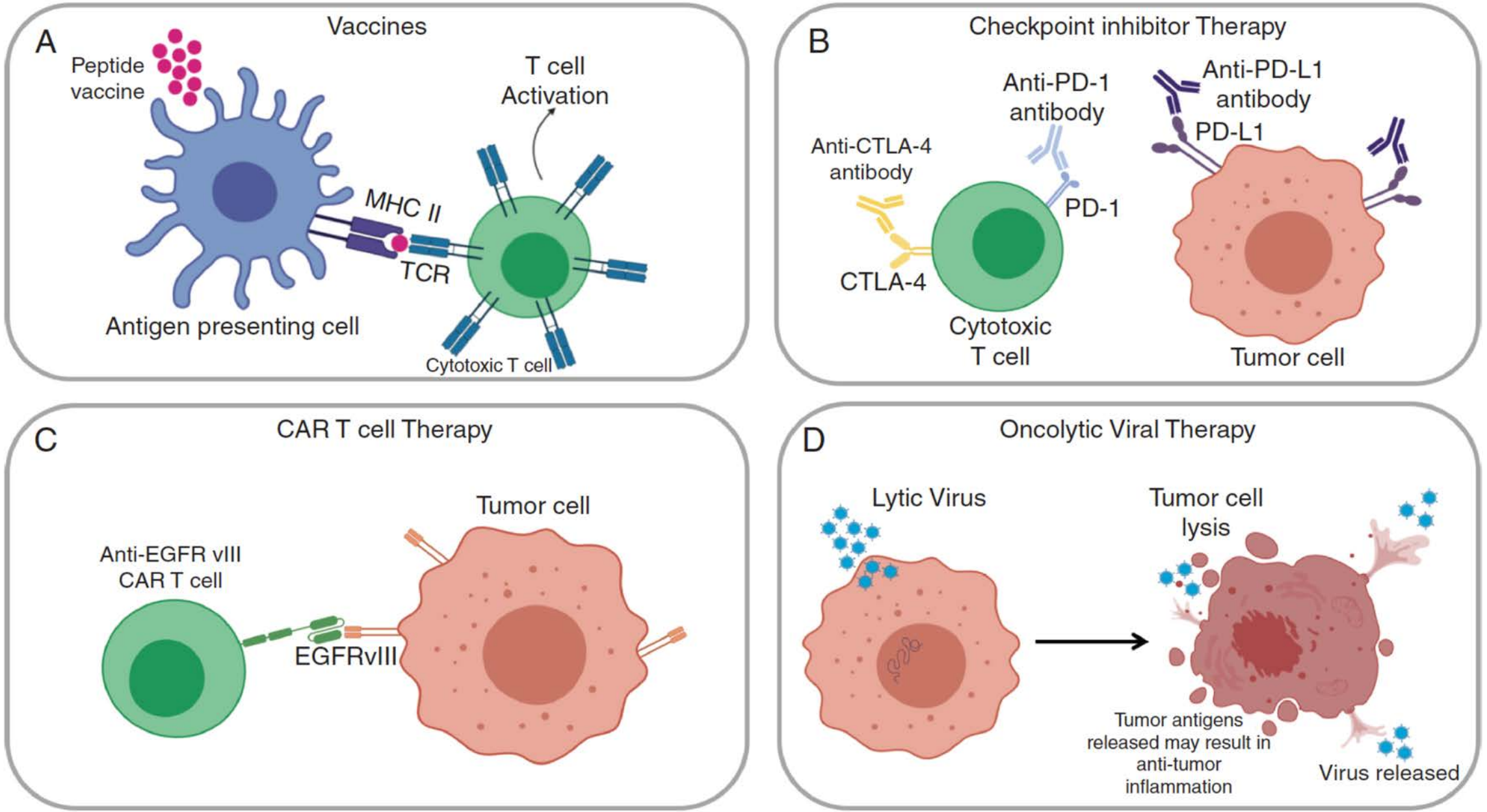
Figure 2. Immune checkpoint targets of monoclonal antibodies.

Zahavi and Weiner, 2020


ORR (%) = 0.5388 ×Any TrAE (%) – 12.25
P < 0.0001
95% CI (0.391 to 0.6865)
Objective Response Rate (%)
0
20
40
60
80
0
20
40
60
80
100
Any Treatment-related Adverse Events (%)


ORR (%) = 0.5559 ×G3-5 TrAE (%) + 13.93
P < 0.0001
95% CI (0.4182 to 0.6936)
Objective Response Rate (%)
0
20
40
60
80

Shen, 2020



Okada review