OLLI SG 492
Human Immune System

Session 9 - May 4, 2022

Today’s Meeting

- Recap
  - Regulatory T cells.
  - Potential causes of autoimmune disease.
- Background on detecting cancer cells.
- Immune Checkpoint Therapy
- CAR T Cell Therapy

Basics of the Immune System

Regulatory T Cells - Development

- Derived from lymphoid progenitor cells in bone marrow.
- Shuffle T cell receptor genes to produce unique T cell receptor.
- Tested in thymus - “Goldilocks process”, not too hot, not too cold, just right:
  - Strong affinity for self peptides results in apoptosis.
  - **Weak** affinity for self peptides results in selection as effector T cell.
  - Intermediate affinity for self peptides results in selection as regulatory T cell.

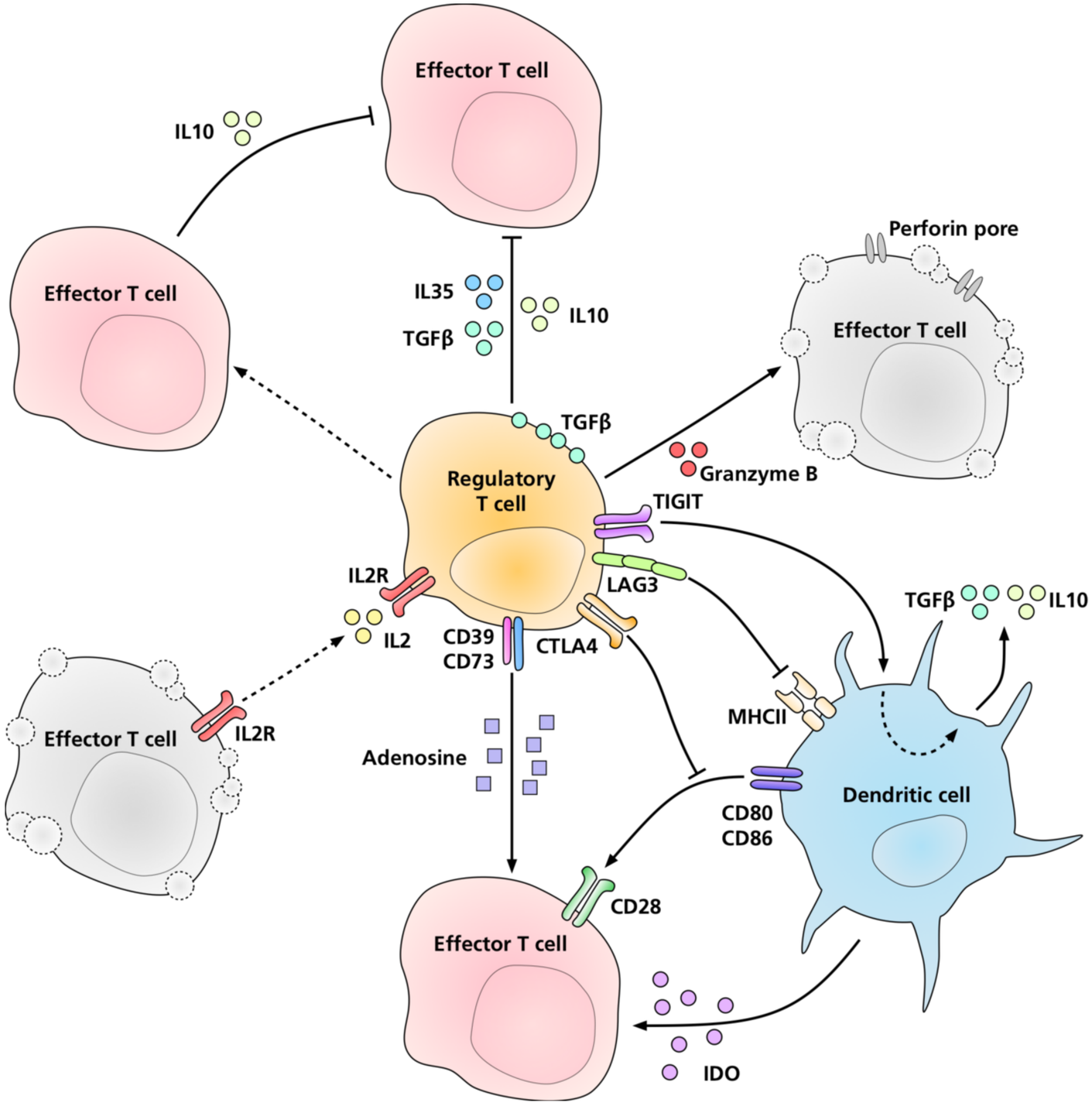
Basics of the Immune System

Regulatory T Cells - Operation

- Modes of operation:
  - Suppression by inhibitory cytokines.
  - Suppression by cytolysis.
  - Suppression by metabolic disruption.
  - Suppression by modulation of dendritic cell maturations or function.
- Recruited to site of infection in same manner as other T cells.

Basics of the Immune System

Regulatory T Cells - Operation



Autoimmunity

Causes

- Experiments performed by two teams in 1993:
  - Subjects were mice genetically engineered to lack T cells.
  - T cells from (normal?) mice were extracted and separated into two types:
    - Naive T cells - had not yet encountered a germ.
    - Switched on T cells - had encountered a germ, memory T cells, and suppressor (regulatory) T cells.
  - Subjects injected only with naive T cells developed autoimmune inflammation.
  - Same subjects subsequently injected with switched on T cells had the autoimmune inflammation stopped.

Autoimmunity

Cause - Davis's Observation

Before Sakaguchi's insight, "…the dogma was that immune cells capable of reacting against the body's own components were weeded out from the system, killed off in the thymus without ever reaching the bloodstream. But Sakaguchi and his contemporaries revealed the situation to be more complex than this. **The system specifically includes cells able to detect the body's own components**, which are there to safeguard against an immune reaction. We now know that this was just the tip of an iceberg because in fact, there are many types of T cell; far greater diversity than can be covered by the crude categories of 'normal' or 'regulatory' cells."

Detection of Cancer Cells

Immune Cells

- Long held belief - cancer was “invisible” to the immune system.
- No “alien” molecule displayed on surface of cancer cell; no molecule for immune cell receptors to detect or bind to.
- Belgian scientist Thierry Boon, established that cancer cells display altered fragments of proteins that can be detected by T cells.
- Natural Killer cells can detect “stress-inducible” proteins on surface of cancer cells.
- “… the immune system helps maintain the integrity of our own body’s cells, screening against detrimental genetic mutations that can arise whenever cells divide.”

Detection of Cancer Cells

Immune Cells

- One way regulatory T cells stop or reduce immune responses is by releasing inhibitory cytokines (IL-10, IL-35, among others).
- Cytotoxic T cells and Helper T cells have receptors for these inhibitory cytokines.
- T cells can detect cancer cells and initiate an immune response.
- Blocking these receptors on T cells already engaged in an immune response against cancer cells would prolong their activity, prolonging the immune response.

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Allison’s insight: stopping the switch-off signal would prolong the immune response against cancer cells.
  - Unleash, not harness, the anti-tumor response.
  - Precision: Only switched on T cells would have their switch-off receptor blocked.
  - Immune Checkpoint Therapy.
- Focus on the CTLA-4 receptor on T cells.

Immune Checkpoint Therapy

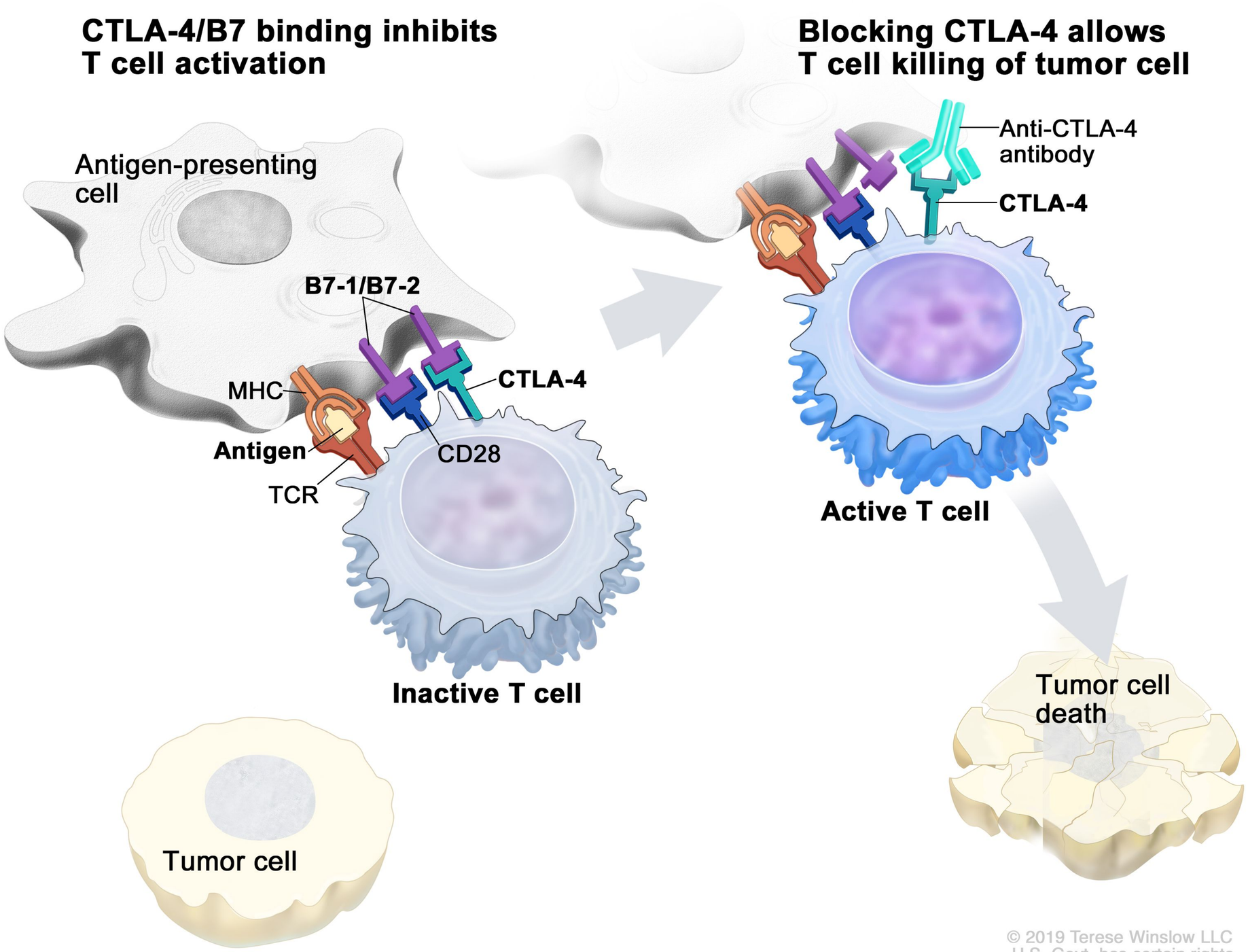
Checkpoint Inhibitor - CTLA-4

- Presence of CTLA-4 receptor:
  - T cells active in an immune response have this receptor.
  - T cells inactive, or resting, do not have this receptor.
  - Only those T cells active in an immune response against cancer would have the CTLA-4 receptor blocked.
- Determining the role of CTLA-4 - first thought to be a stimulator of an immune response.

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

Immune checkpoint inhibitor. Checkpoint proteins, such as B7-1/B7-2 on antigen-presenting cells (APC) and CTLA-4 on T cells, help keep the body's immune responses in check. When the T-cell receptor (TCR) binds to antigen and major histocompatibility complex (MHC) proteins on the APC and CD28 binds to B7-1/B7-2 on the APC, the T cell can be activated. However, the binding of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state so they are not able to kill tumor cells in the body (left panel). Blocking the binding of B7-1/B7-2 to CTLA-4 with an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumor cells (right panel).



Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Longer Checkpoint Inhibitor Therapy Video.
- Shorter Checkpoint Inhibitor Therapy Video.

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Proof that CTLA-4 switched off immune responses:
  - Antibodies were developed to block the CTLA-4 receptor.
  - Jeff Bluestone’s lab in 1994 showed that blocking the CTLA-4 receptor caused T cells to react more, not less - produced a stronger T cell reaction.
  - This showed that CTLA-4 was not a stimulator of immune reactions, but an off-signal, shutting down an immune reaction.
- Experiments in Allison’s lab came to the same conclusion.

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Despite both Allison and Bluestone arriving at the same conclusion, skepticism remained.
- Definitive proof involved experiments with genetically-modified mice that lacked the CTLA-4 receptor.
    - These mice died at a young age from “massive expansion” of immune cells, producing toxic levels of inflammation.
    - Showed that CTLA-4 was vitally important for switching off an immune response.

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Allison’s lab studied CTLA-4 and cancer in mice:
  - Injected the antibody into mice with bowel cancer.
  - Small study showed complete regression of the tumors.
  - Larger, blind study showed, with a lag of two weeks, that the tumors began to regress and eventually completely disappeared.
  - Astonishing: Blocking a single molecule could lead to complete tumor regression.
  - Studies on other cancers in mice were successful.
  - “Good news for mice!”

Immune Checkpoint Therapy

Checkpoint Inhibitor - CTLA-4

- Human clinical trials:
  - Mixed results. Some tumors increased in size initially as a result of immune cells infiltrating the tumor.
  - Later tumors shrank.
  - Led to a change in the WHO criteria for trial success - Immune-Related Response Criteria.
  - Clinical trial with melanoma patients resulted in survival rates that increased from 6 to 10 months.
  - March 2011: FDA approval of Yervoy.

Immune Checkpoint Therapy

Checkpoint Inhibitor - PD-1

- Another checkpoint to switch-off immune response - PD-1:
  - Discovered in 1992 by Japanes scientist Tasuku Honjo.
  - T cell receptor originally thought to be involved in programmed cell death.
  - Mice genetically-engineered to lack the PD-1 receptor had a more vigorous immune system, and older mice developed autoimmune diseases.
  - Showed that PD-1 sends a switch-off signal to immune cells.
  - Like CTLA-4, only immune cells switched on to participate in an immune response exhibit this receptor.

Immune Checkpoint Therapy

Checkpoint Inhibitor - PD-1

- Complementary roles of CTLA-4 and PD-1:
  - PD-1 locks onto proteins induced on the surface of cells exposed to inflammation.
  - CTLA-4 locks onto proteins of other immune cells, like dendritic cells.
  - PD-1 is important in dialing down an ongoing local immune response.
  - CTLA-4 is more important in dampening the system as a whole in order to prevent a body-wide type of autoimmune disease.

Immune Checkpoint Therapy

Checkpoint Inhibitor - PD-1

- Clinical Trials with PD-1:
  - Blocking PD-1 was more effective than blocking CTLA-4 in melanoma.
  - Fewer adverse side effects.
  - Other hard to treat cancers regressed with PD-1.
- Results from PD-1 trials showed that the results from CTLA-4 trials were not a fluke.
- Ensuring the immune response doesn’t turn itself off is a viable therapy.
- Allison and Honjo won a Nobel Prize in 2018.

Immune Checkpoint Therapy

Biomarkers

- Discovery of more checkpoint inhibitors (“brakes”) increased the importance of finding out who had the best chance of responding to them.
- Measures of the potential for responding are “biomarkers.” E.G.:
  - Which brake receptors are present on the surface of immune cells.
  - Determining whether or not a tumor cell contains the proteins that trigger particular brake receptors on immune cells.
  - “The quest for predictive biomarkers is important but as a research field it is still young.”

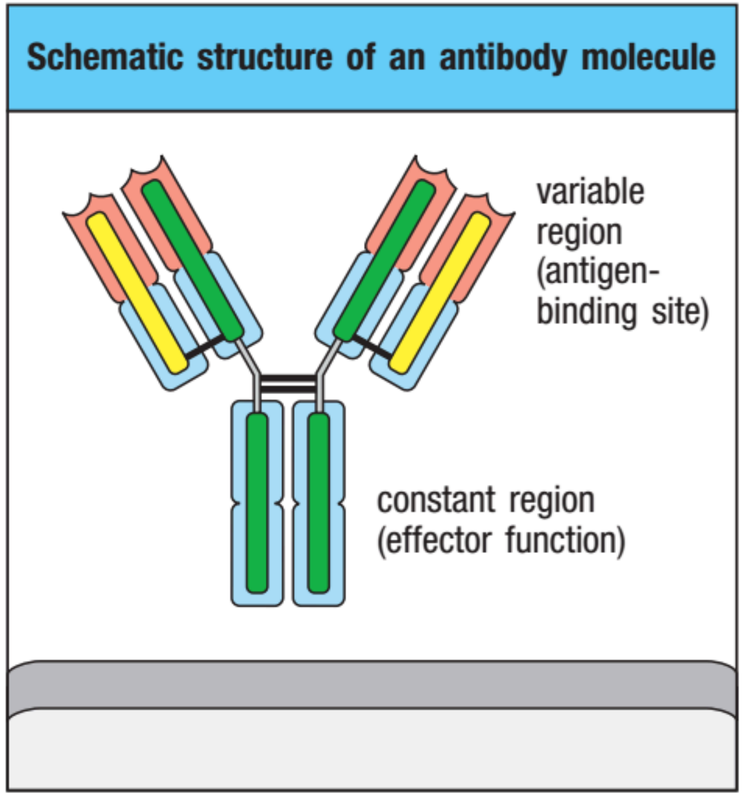
Immune Checkpoint Therapy

Checkpoint Inhibitors

- Complications of using antibodies:
  - The front-end of the antibody may bind to a switch-off receptor like CTLA-4, but the back-end could attract immune cells to destroy the T cell.
  - The result would be a kill-off of the immune cells needed to destroy cancer cells.
  - Regulatory T cells have high levels of CTLA-4 on their surface. Implication: the antibodies may be targeting regulatory T cells for destruction.
  - "… the precise way in which an antibody against CTLA-4 helps cancer patients is **not entirely clear**…"

Basics of the Immune System

Antigen Receptors



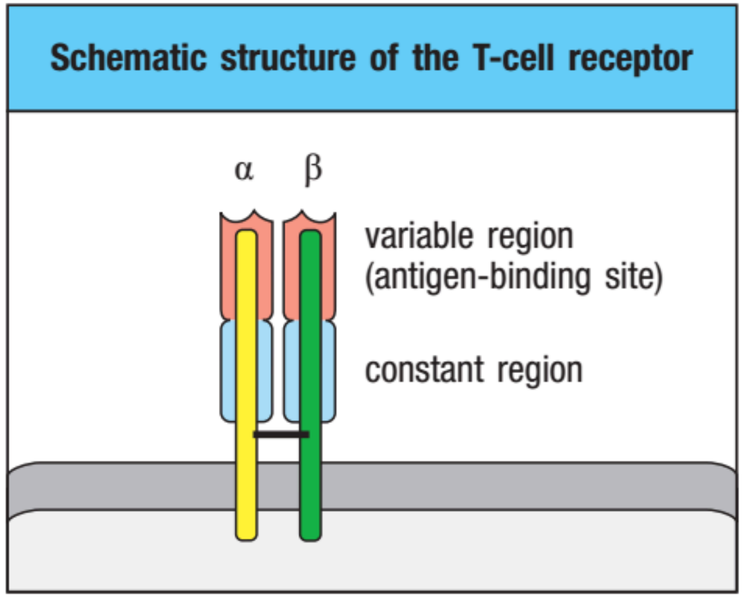


Fig. 1.13 Schematic structure of antigen receptors. Upper panel: an antibody molecule, which is secreted by activated B cells as an antigen-binding effector molecule. A membrane-bound version of this molecule acts as the B-cell antigen receptor (not shown). An antibody is composed of two identical heavy chains (green) and two identical light chains (yellow). Each chain has a constant part (shaded blue) and a variable part (shaded red). Each arm of the antibody molecule is formed by a light chain and a heavy chain, with the variable parts of the two chains coming together to create a variable region that contains the antigen-binding site. The stem is formed from the constant parts of the heavy chains and takes a limited number of forms. This constant region is involved in the elimination of the bound antigen. Lower panel: a T-cell antigen receptor. This is also composed of two chains, an α chain (yellow) and a β chain (green), each of which has a variable and a constant part. As with the antibody molecule, the variable parts of the two chains create a variable region, which forms the antigen-binding site. The T-cell receptor is not produced in a secreted form.

Immune System - Highlights

Action of Antibodies

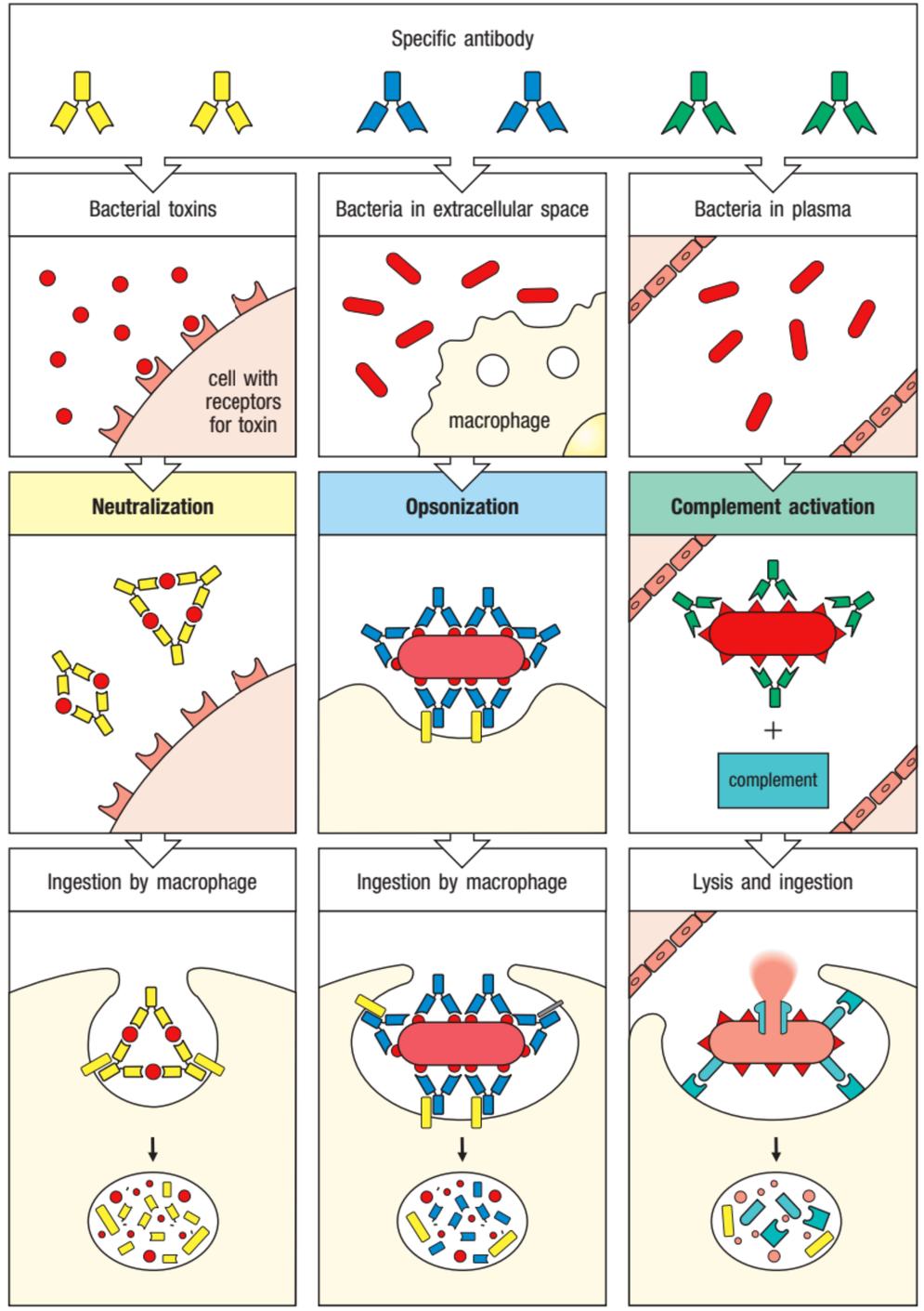


Fig. 1.28 Antibodies can participate in host defense in three main ways. The left panels show antibodies binding to and neutralizing a bacterial toxin, thus preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin:antibody complex cannot. Antibodies also neutralize complete virus particles and bacterial cells by binding and inactivating them. The antigen:antibody complex is eventually scavenged and degraded by macrophages. Antibodies coating an antigen render it recognizable as foreign by phagocytes (macrophages and neutrophils), which then ingest and destroy it; this is called opsonization. The center panels show opsonization and phagocytosis of a bacterial cell. Antibody first binds to antigens (red) on the bacterial cell through the variable regions. Then the antibody's Fc region binds to Fc receptors (yellow) expressed by macrophages and other phagocytes, facilitating phagocytosis. The right panels show activation of the complement system by antibodies coating a bacterial cell. Bound antibodies form a platform that activates the first protein in the complement system, which deposits complement proteins (blue) on the surface of the bacterium. This can lead in some cases to formation of a pore that lyses the bacterium directly. More generally, complement proteins on the bacterium can be recognized by complement receptors on phagocytes; this stimulates the phagocytes to ingest and destroy the bacterium. Thus, antibodies target pathogens and their toxic products for disposal by phagocytes.

CAR T Cell Therapy

Development

- Checkpoint inhibitors don’t work for everyone.
- Goal: Combination therapy that makes sure a patient has “immune cells capable of detecting their cancer.”
- Carl June of Univ. of Pennsylvania in **2011**:
  - Extracted T cells from a cancer patient.
  - Genetically manipulated the T cells to add a new receptor.
  - The receptor was designed to target the patients cancer.

CAR T Cell Therapy

Development and Approval

- The added receptor was a “Chimeric Antigen Receptor.”
- The receptor is an antibody - the front end locks onto cancer cells, the back end triggers T cells to kill.
- A patient’s own T cells were reprogrammed to kill their own cancer cells.
- Two of the first three patients to receive this treatment experienced complete remission.
- August 2017, FDA approved use of CAR T cells for one type of cancer, and a few weeks later for another.

Up Next

- Review and summary - What we know about the human immune system, how it works, and what we don’t know.
- Q & A on any study group topic.
- Observations on the novel coronavirus and covid-19.