OLLI SG 492
Human Immune System

Session 10 - May 11, 2022

Today’s Meeting

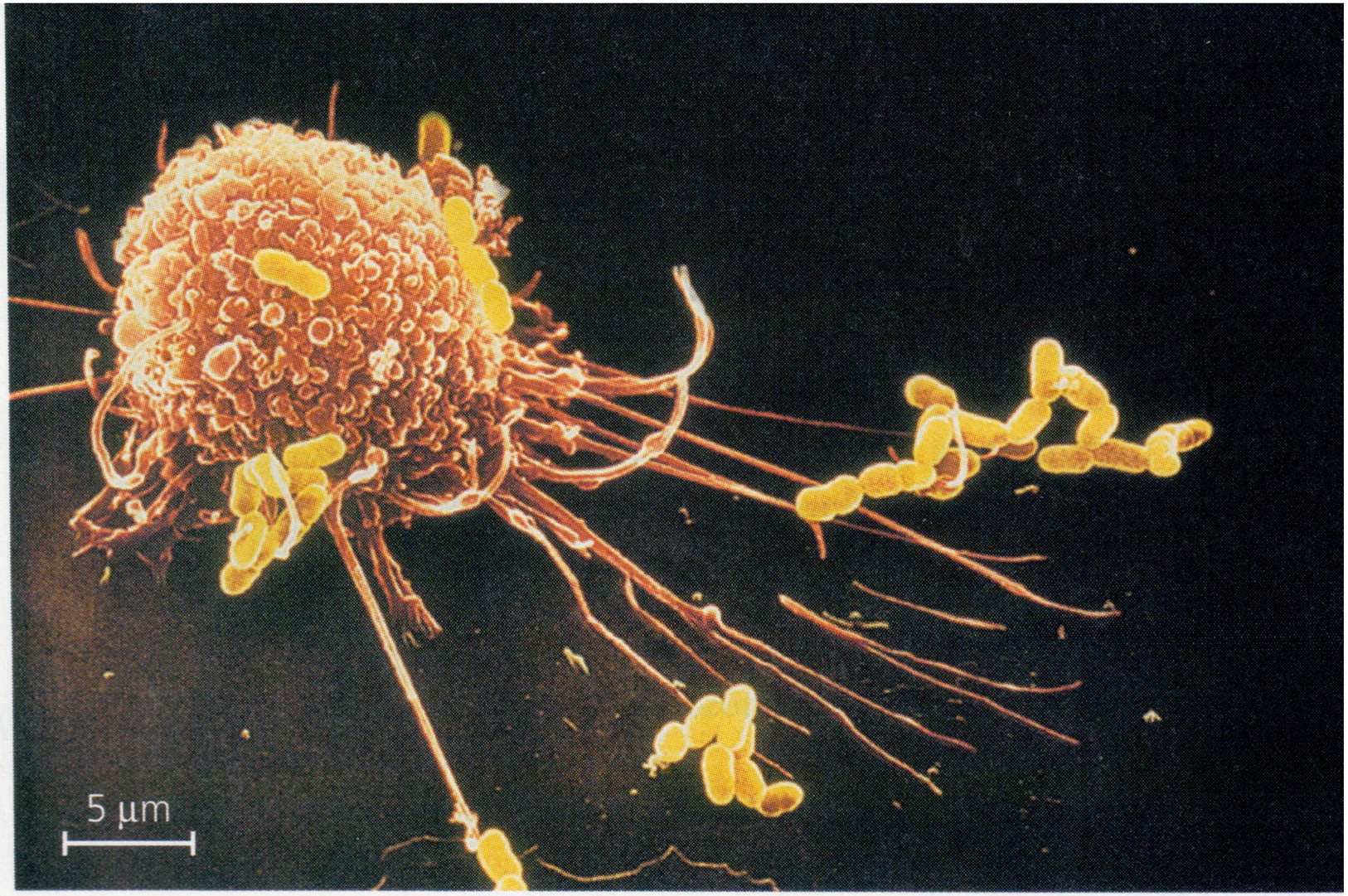
- Takeaways on the Immune System.
- Q&A on the Immune System.
- Overview of the novel coronavirus and Covid-19.

Takeaways

Innate Immune System

- “First Line of Defense” against pathogens.
- Macrophage, neutrophil and dendritic cells.
- Inflammatory response.

Takeaways
Macrophages



▲ **Figure 6.31 The emergence of cellular functions.** The ability of this macrophage (brown) to recognize, apprehend, and destroy bacteria (yellow) is a coordinated activity of the whole cell. Its cytoskeleton, lysosomes, and plasma membrane are among the components that function in phagocytosis (colorized SEM).

Takeaways

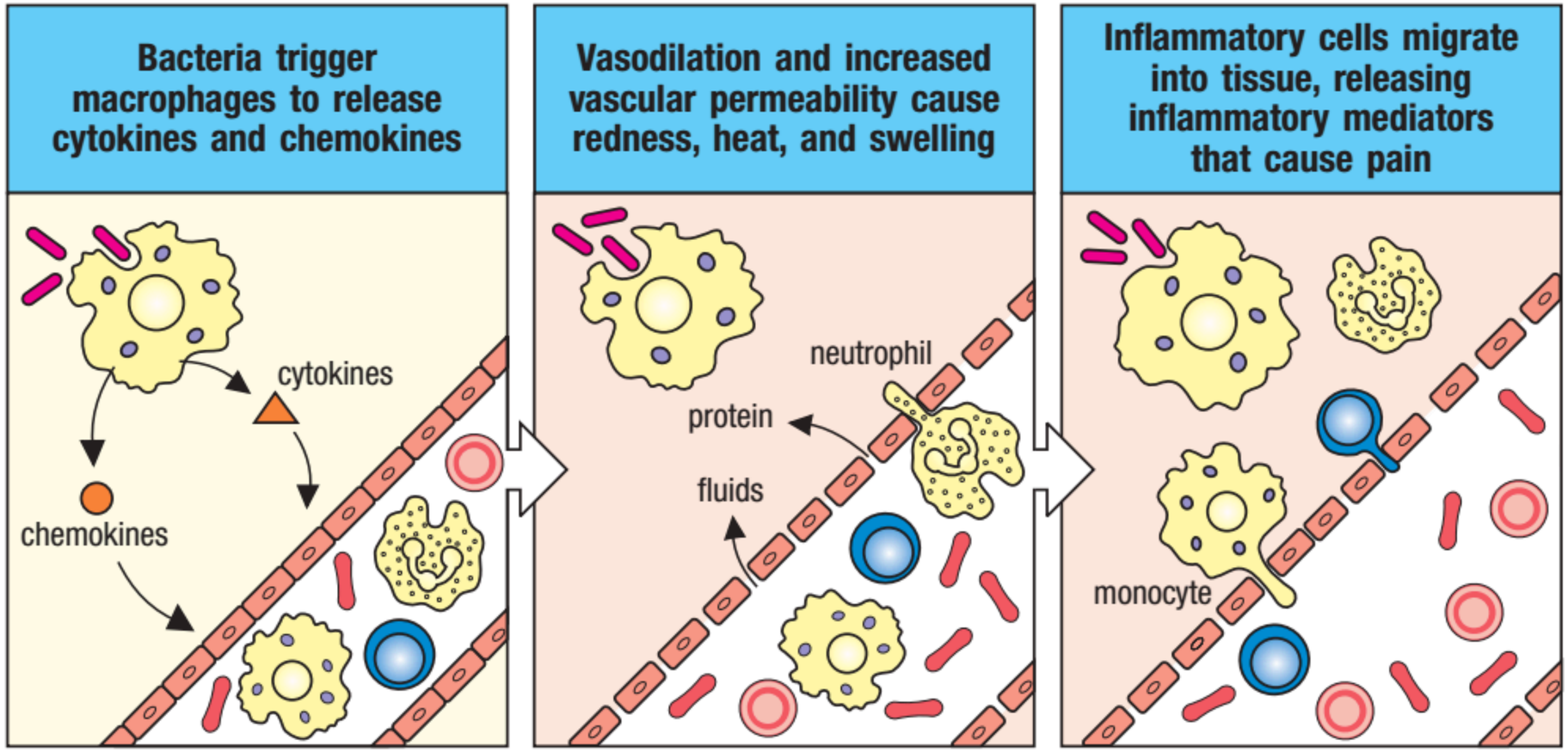
Macrophages and Cytokines

- Release of cytokines by a macrophage - Video

Takeaways

Inflammatory Response

Fig. 1.10 Infection triggers an inflammatory response. Macrophages encountering bacteria or other types of microorganisms in tissues are triggered to release cytokines (left panel) that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues (center panel). Macrophages also produce chemokines, which direct the migration of neutrophils to the site of infection. The stickiness of the endothelial cells of the blood vessel wall is also changed, so that circulating cells of the immune system adhere to the wall and are able to crawl through it; first neutrophils and then monocytes are shown entering the tissue from a blood vessel (right panel). The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes can also contribute to inflammation.



Takeaways

Timeline of the Immune Response

Phases of the immune response			
Response		**Typical time after infection to start of response**	**Duration of response**
Innate immune response	Inflammation, complement activation, phagocytosis, and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Elimination of pathogen by effector cells and antibody	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

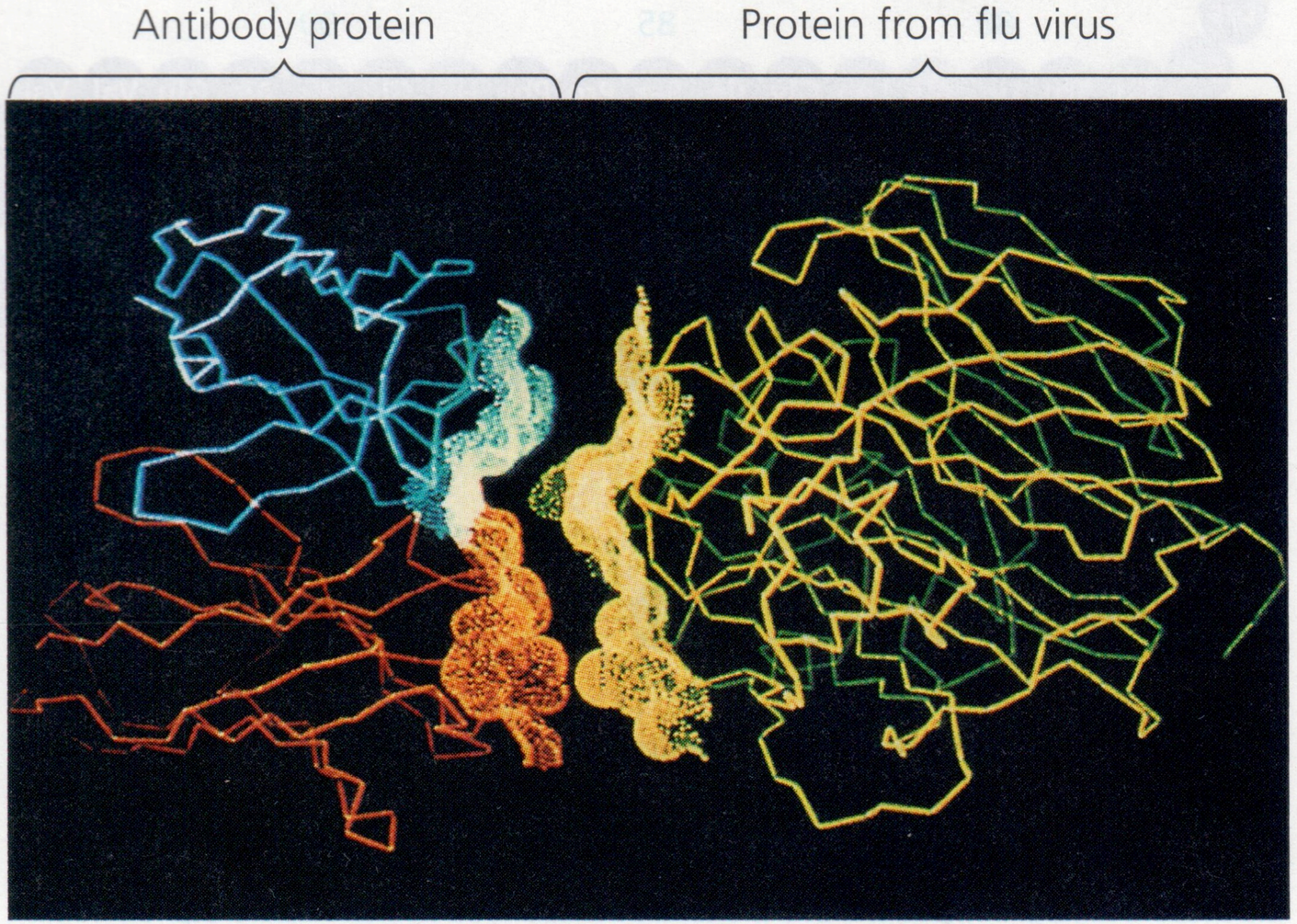
Takeaways

Receptors and Signaling Pathways

- Protein shapes.
- Pattern Recognition Receptors and Antigen Specific Receptors.
  - Detection of pathogens.
- Intracellular signaling pathways.
- Extracellular signaling pathways.
  - Cytokines and Chemokines.
  - Chemical/molecular concentration gradients.

Takeaways

Protein Binding

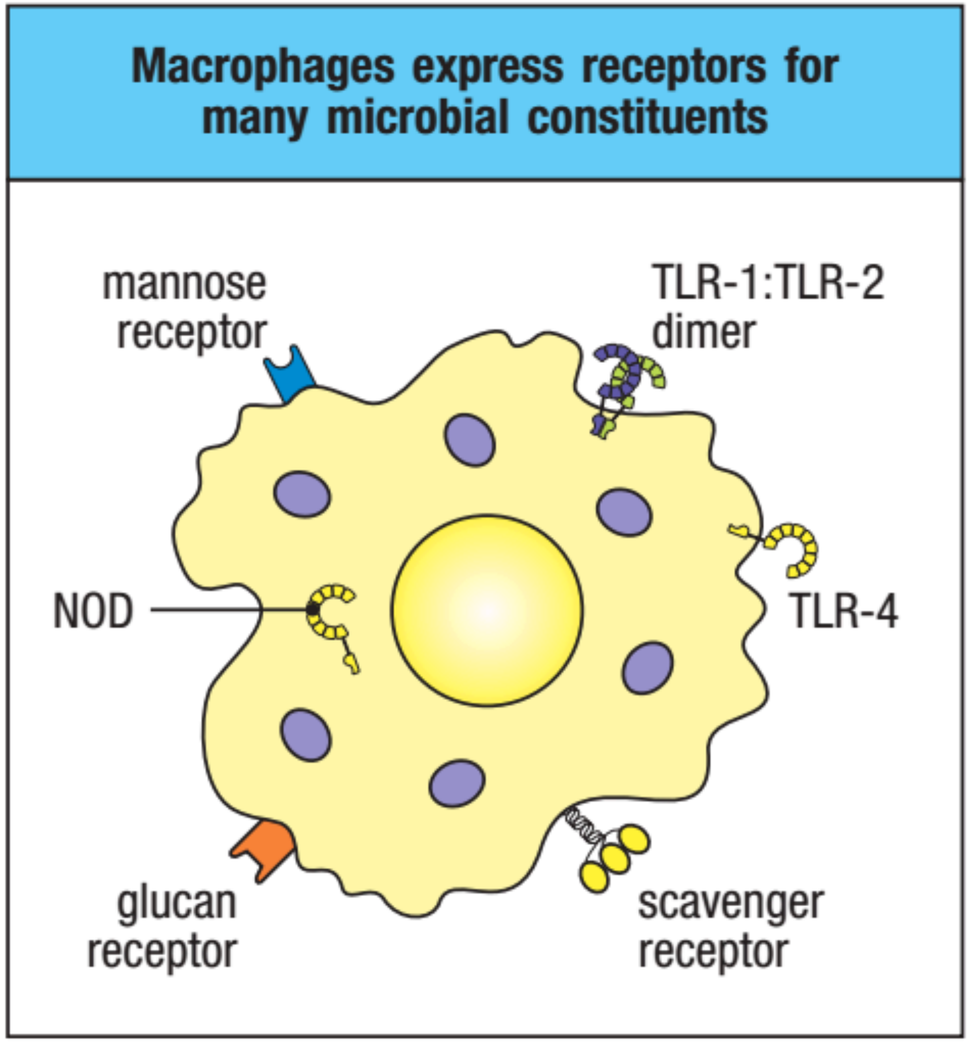


▲ **Figure 5.17 An antibody binding to a protein from a flu virus.** A technique called X-ray crystallography was used to generate a computer model of an antibody protein (blue and orange, left) bound to a flu virus protein (green and yellow, right). Computer software was then used to back the images away from each other, revealing the exact complementarity of shape between the two protein surfaces.

Takeaways

Macrophage Receptors

Fig. 1.9 Macrophages express a number of receptors that allow them to recognize different pathogens. Macrophages express a variety of receptors, each of which is able to recognize specific components of microbes. Some, like the mannose and glucan receptors and the scavenger receptor, bind cell-wall carbohydrates of bacteria, yeast, and fungi. The Toll-like receptors (TLRs) are an important family of pattern recognition receptors present on macrophages, dendritic cells, and other immune cells. TLRs recognize different microbial components; for example, a heterodimer of TLR-1 and TLR-2 binds certain lipopeptides from pathogens such as Gram-positive bacteria, while TLR-4 binds both lipopolysaccharides from Gram-negative and lipoteichoic acids from Gram-positive bacteria.



Takeaways

Antigen-Specific Receptors and MHC

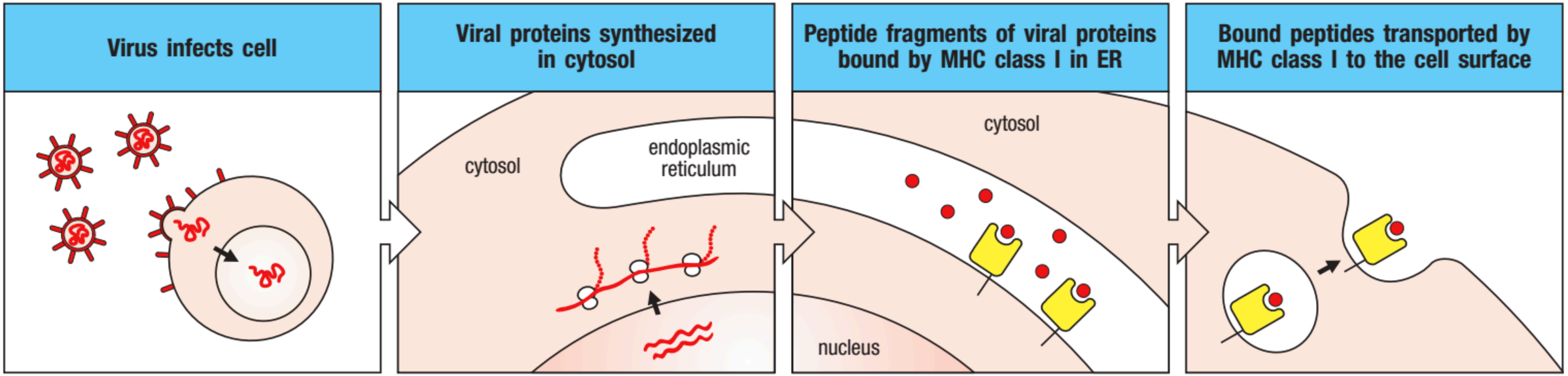
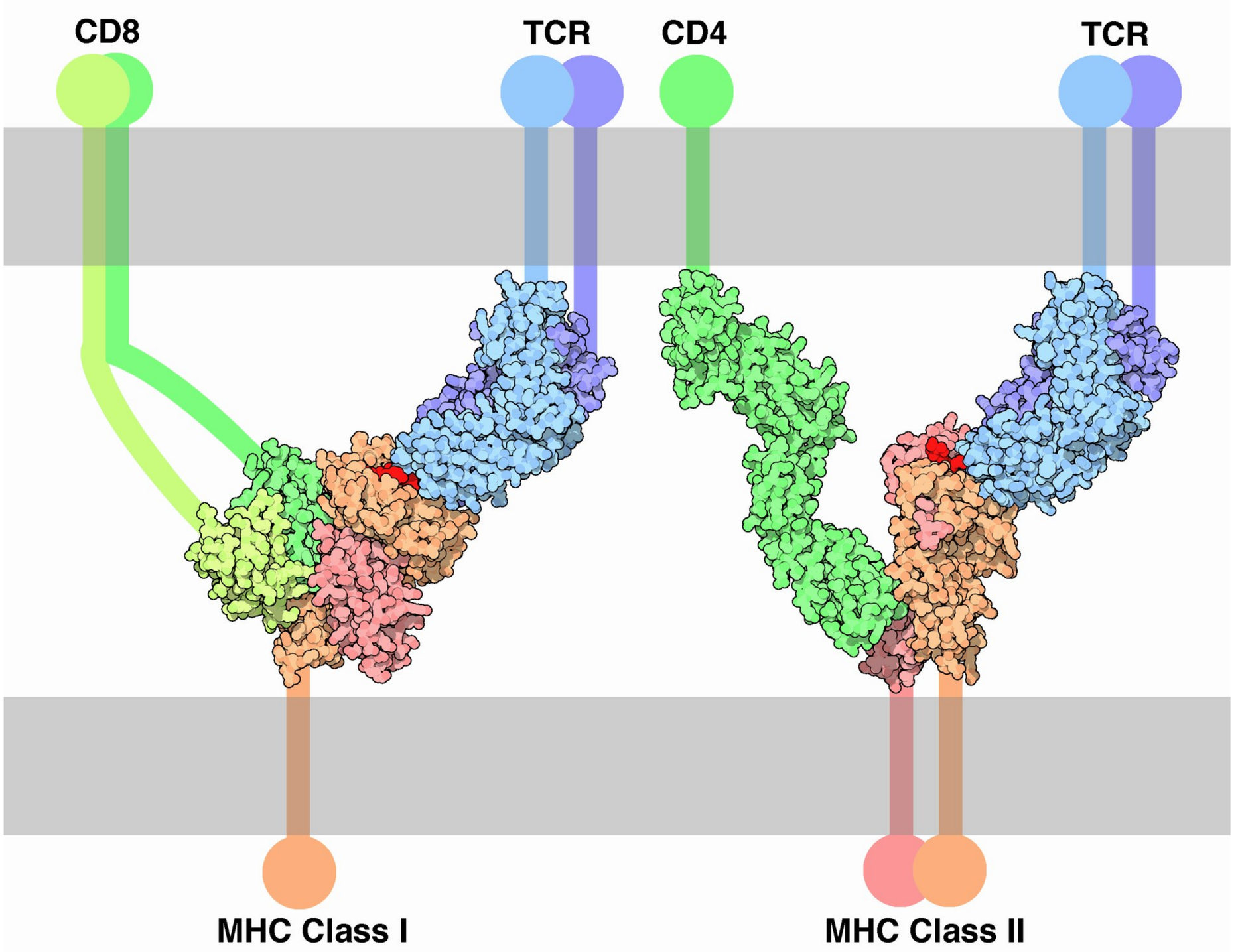


Fig. 1.30 MHC class I molecules present antigen derived from proteins in the cytosol. In cells infected with viruses, viral proteins are synthesized in the cytosol. Peptide fragments of viral proteins are transported into the endoplasmic reticulum (ER), where they are bound by MHC class I molecules, which then deliver the peptides to the cell surface.

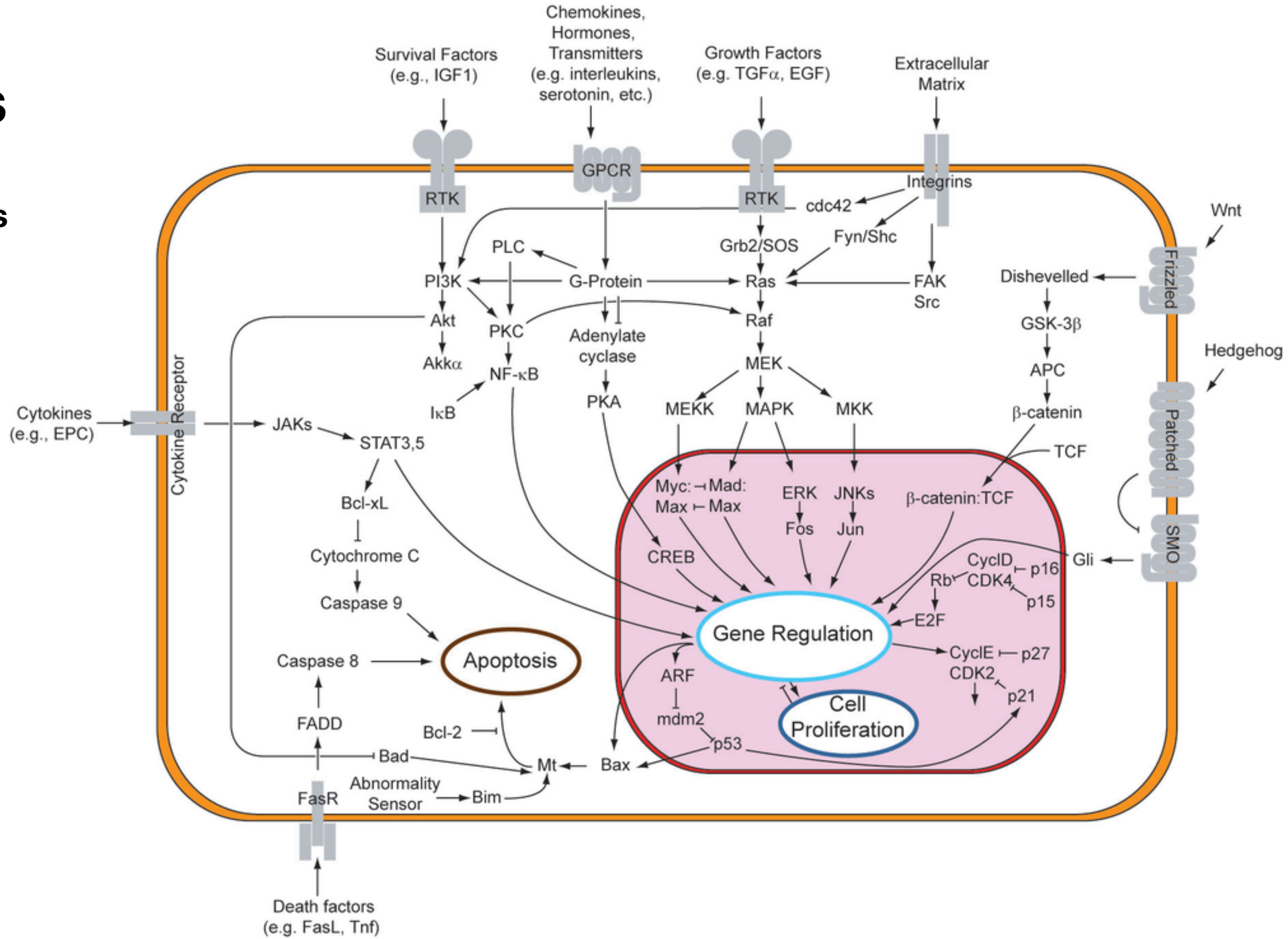
Takeaways

Antigen-Specific Receptors



Takeaways

Intracellular Signaling Pathways



Takeaways

Non-cellular Defenses

- Complement.
- Kurzgesagt video on Complement.
- Anti-microbial molecules and enzymes in sweat, tears, and saliva.

Takeaways

Functions of the Immune System… and Stress and Ageing

- Fighting Infections… and maintaining the integrity of the body.
- Benefits of fever
- Cortisol and stress.
- Accumulated cellular damage from… life.
- Decline of the immune system function with age.
- Increase in autoimmune diseases - in all age groups, but especially the elderly.

Takeaways

Functions of the Immune System

- Maintain the integrity of the body:
  - Both innate and adaptive immune cells can detect and destroy damaged or dead cells. Damaged cells present molecules on their surface that indicate stress or damage.
  - The “Goldilocks process” of selecting T cells allows T cells that have an affinity for self antigens (weak or intermediate) to survive and play a role in the immune response.
  - Negative effect: potential for causing autoimmune diseases.
  - Positive effect: potential for fighting cancer.

Takeaways

Stress and the Immune System

- Cortisol levels change dramatically with stress, dampening our immune system.
- If stress persists, the immune system may stay weakened.
- People under prolonged stress:
  - Suffer worse from viral infections.
  - Take longer to heal wounds.
  - Respond less well to vaccinations.
- The bad effect of stress on health is the best established link between lifestyle and the immune system.

Takeaways

Ageing

- “Inflamm-ageing”:
  - Cytokines, clotting factors, and inflammatory molecules are found at higher levels in the elderly without overt signs of infection.
  - May result from accumulation of damaged or senescent cells.
  - Effect is that immune system is less able to discriminate between pathogens and the body’s own cells and tissues.
  - Further effect is that immune system is weak at detecting novel pathogens.
- While it may be easier to trigger an immune response in the elderly, the response is less discriminating.

Takeaways

Immune System and Immunotherapy

- Role of Regulatory T Cells in autoimmune diseases.
- Role of the microbiome in autoimmune diseases… and hygiene hypothesis.
- Role of Regulatory T Cells in cancer.
- Cancer Immunotherapies.
  - Checkpoint Inhibitor Therapy - CTLA-4 and PD-1.
  - CAR T Cell Therapy.

Takeaways

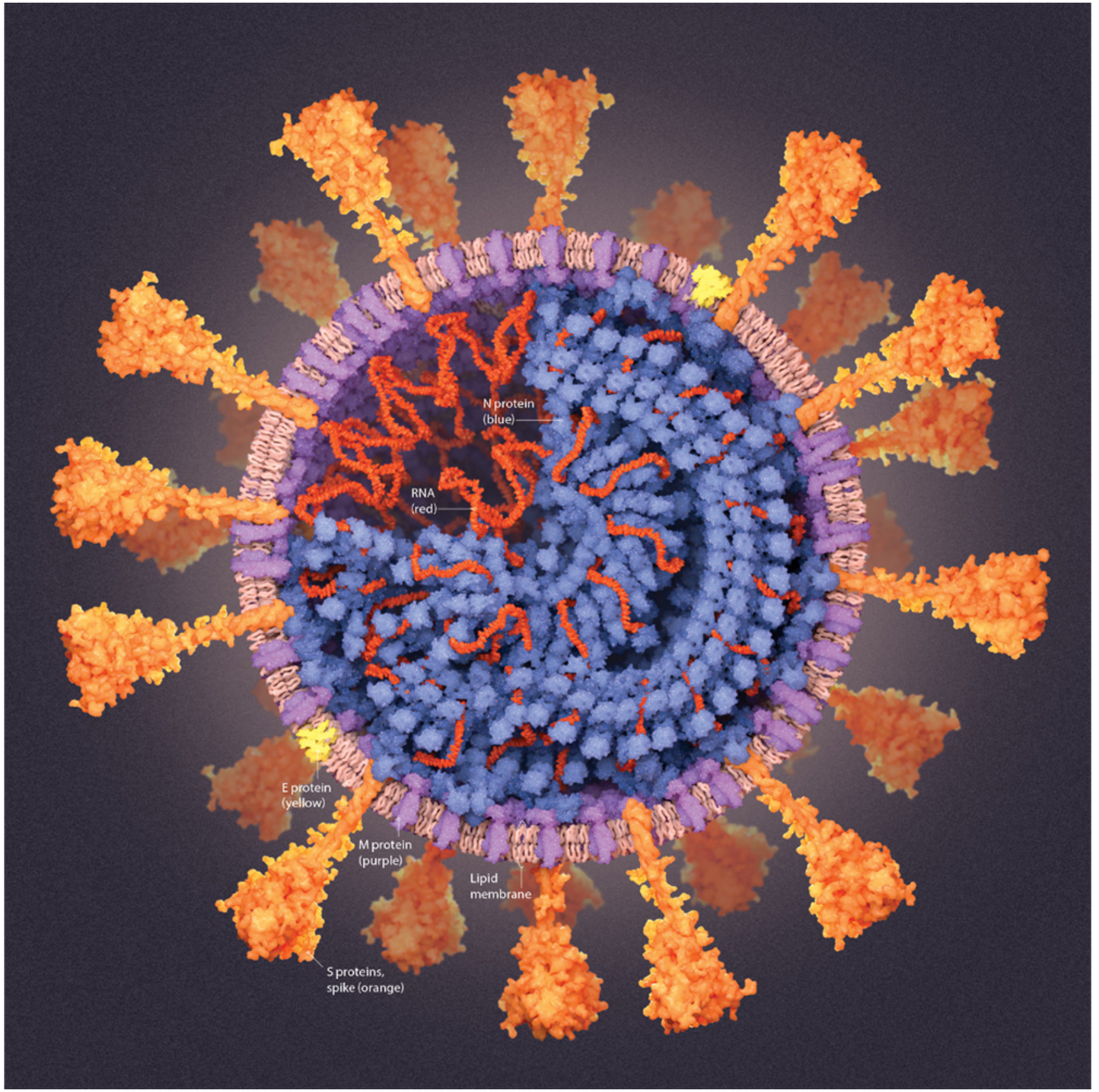
Nirvana on the Horizon?

“The reason that we’ve begun to triumph – why it is not hyperbole to suggest that we are at the dawn of a health revolution – is that we have now identified some of the hubs in the system: cells and molecules that, when targeted with drugs that boost or halt their activity, dramatically shift the behaviour of the system as a whole. We saw this with anti-cytokines. Blocking only one cytokine, TNF, for example, can alleviate the inflammation that underlies arthritis by halting an entire cascade of effects – in this case by severing the feedback loop in which immune cells keep triggering one another into action, leading to an autoimmune attack. When drugs, foods, prebiotics or probiotics are developed to impact the behaviour or numbers of regulatory T cells, which are undoubtedly also a hub in the system, we will have new treatments for allergies and other autoimmune diseases.”

Coronavirus Cross Section

Gene Machine

A SARS-CoV-2 virus particle wafting into a person's nose or mouth is about 100 nanometers in diameter—visible only with an electron microscope. It is a near sphere of protein (cross section shown) inside a fatty membrane that protects a twisting strand of RNA—a molecule that holds the virus's genetic code. Proteins called "S" form spikes that extend from the surface and grab onto a human cell, hundreds of times larger, so the particle, or virion, can slip inside; the crown, or corona, appearance gives the virus its name. Structural proteins—N, M and E—move inside the cell, where they help new virions form.



Coronavirus

- Historical background on coronaviruses:
  - One of many viruses that have made the “jump” from animals to humans.
  - Severe Acute Respiratory Syndrome (SARS) first appeared in China in 2002. Official name: SARS-CoV. Source: Bats.
  - SARS killed 10% of infected.
  - Middle Eastern Respiratory Syndrome (MERS) appeared in Saudi Arabia in 2012. Official name: MERS-CoV. Source: Bats (through camels).
  - Current pandemic: Official name SARS-CoV2. First appeared in China 2019. Source: ? (Bats?). Disease resulting from infection: Covid-19.

Coronavirus

- Process of infection:
  - SARS-CoV-2 spike proteins attach to ACE2 receptors on surface of cells in air passageways.
  - ACE2 - Angiotensin-converting enzyme 2. Lowers blood pressure by converting vasoconstrictor peptides into vasodilator peptides.
  - Promising drug for treating cardiovascular disease.
  - Often found on cell membranes of intestine, kidney, and heart cells, among others.
  - Some expression in cells of the respiratory system

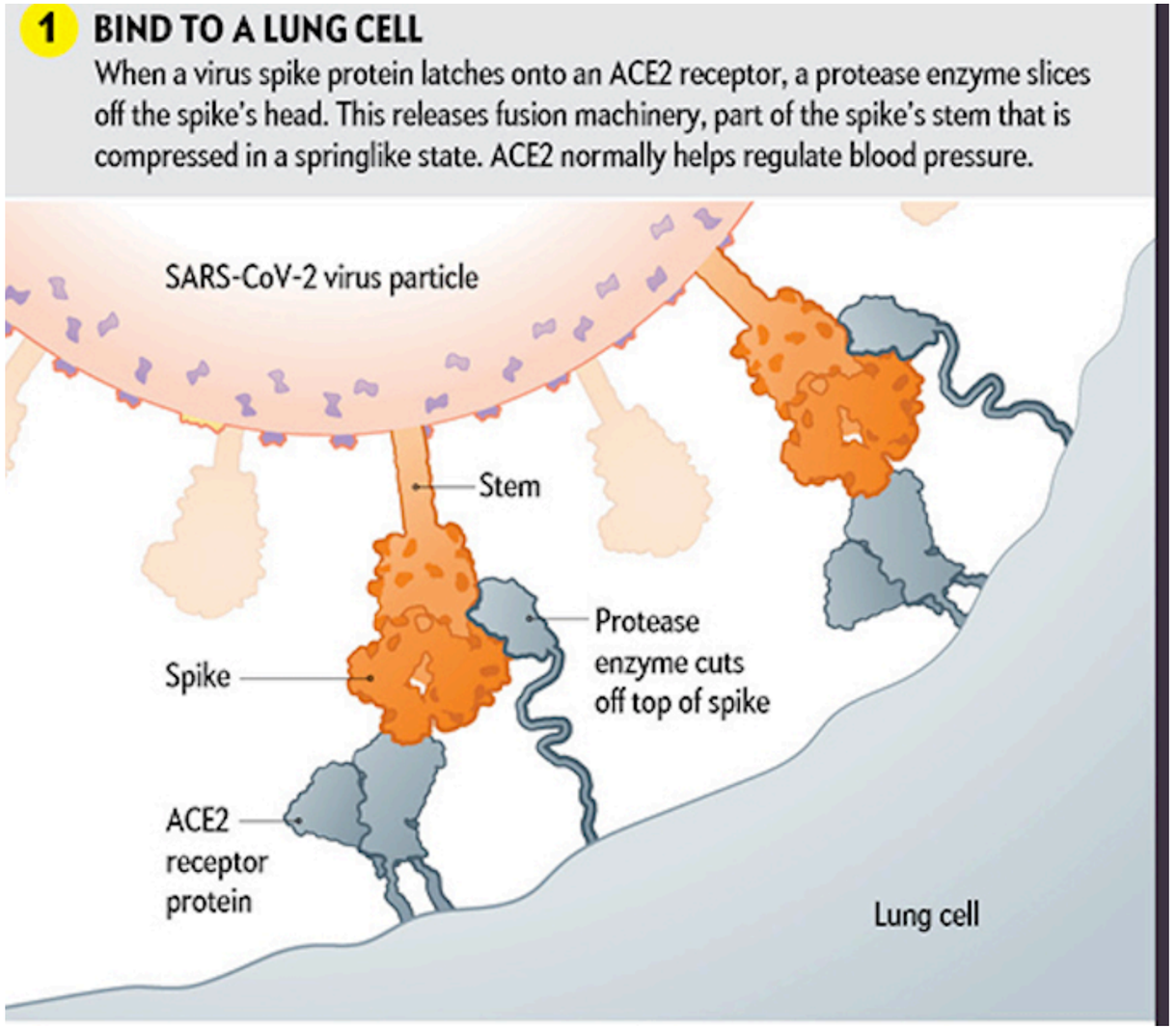
Coronavirus

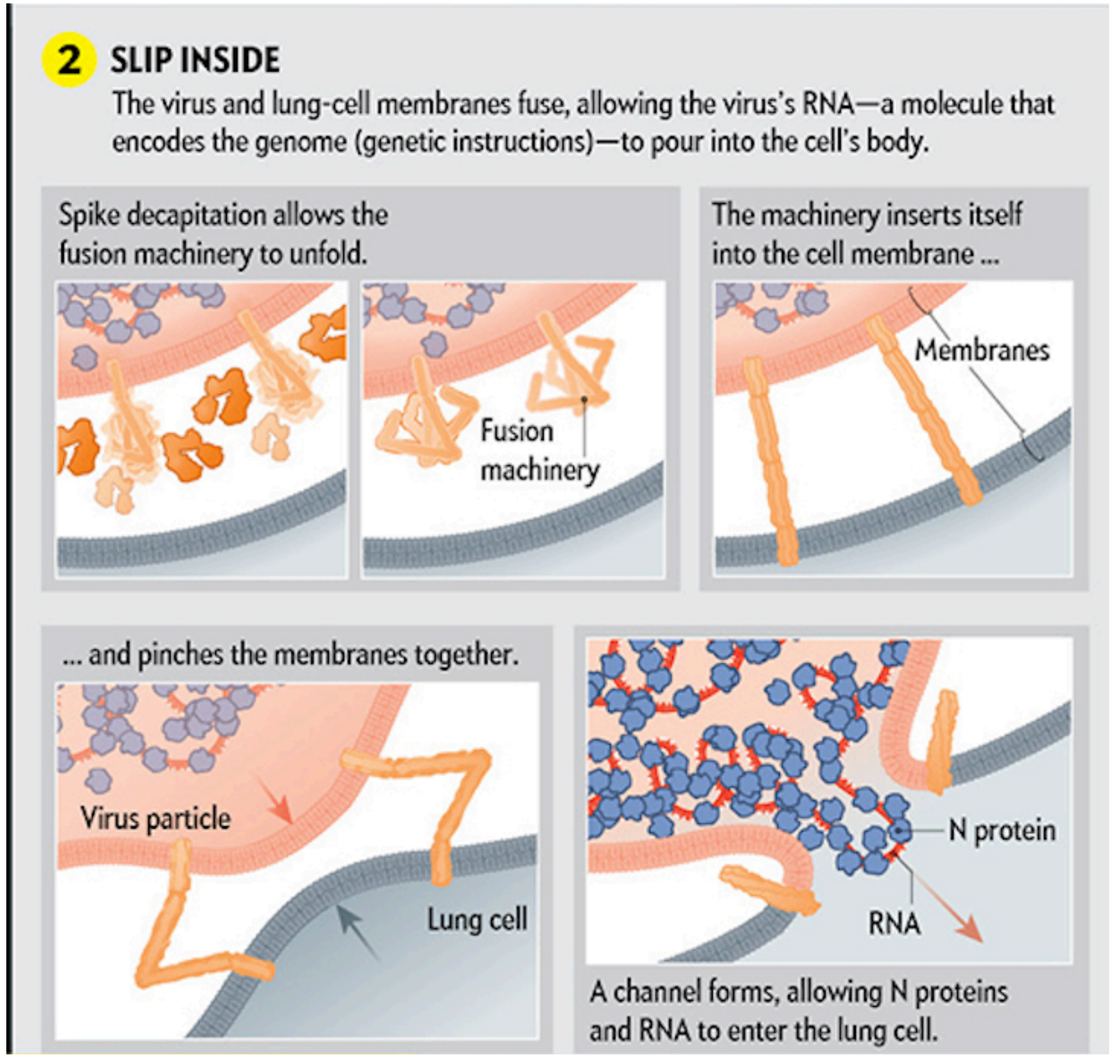
Reference Material

- Video on Cytokines.
- Video on infection of cell by coronavirus. (Begin at 39:00 minutes)
- Article in New England Journal of Medicine on Cytokine Storms.

Coronavirus

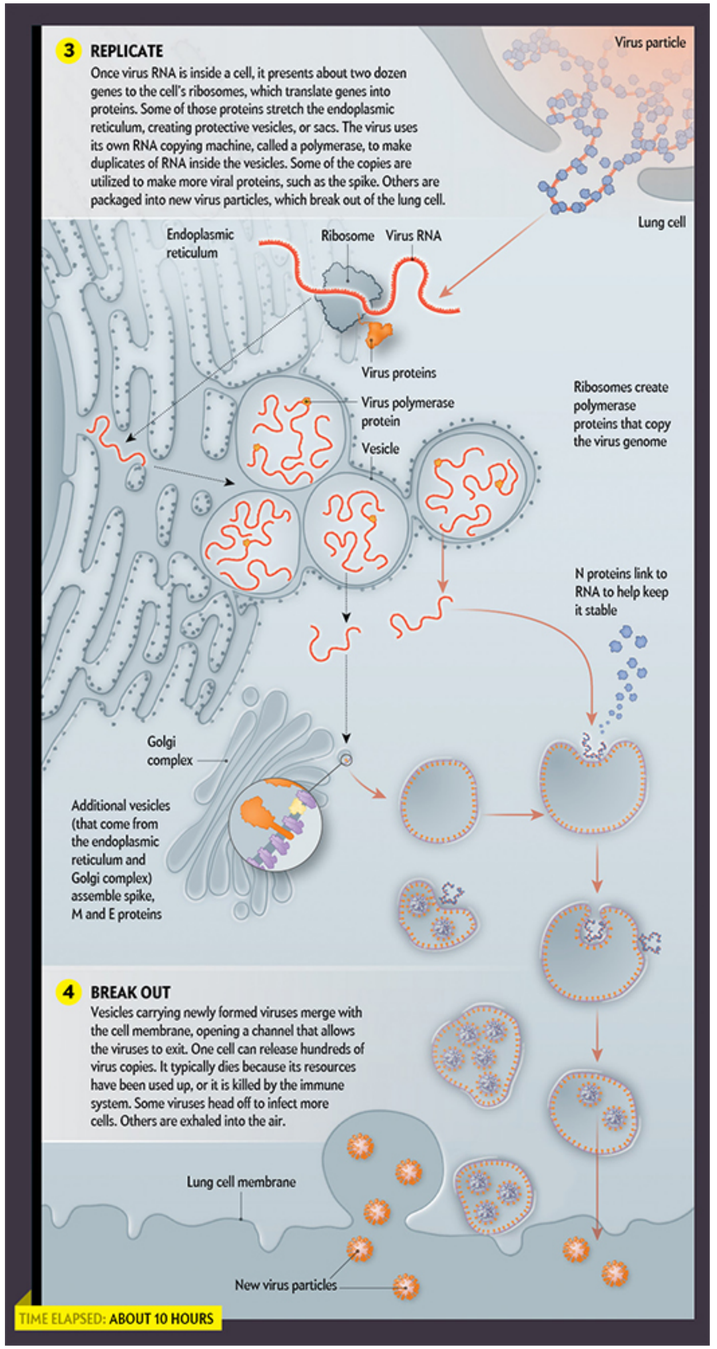
Elapsed Time - 10 Minutes





Coronavirus

Elapsed Time - About 10 Hours



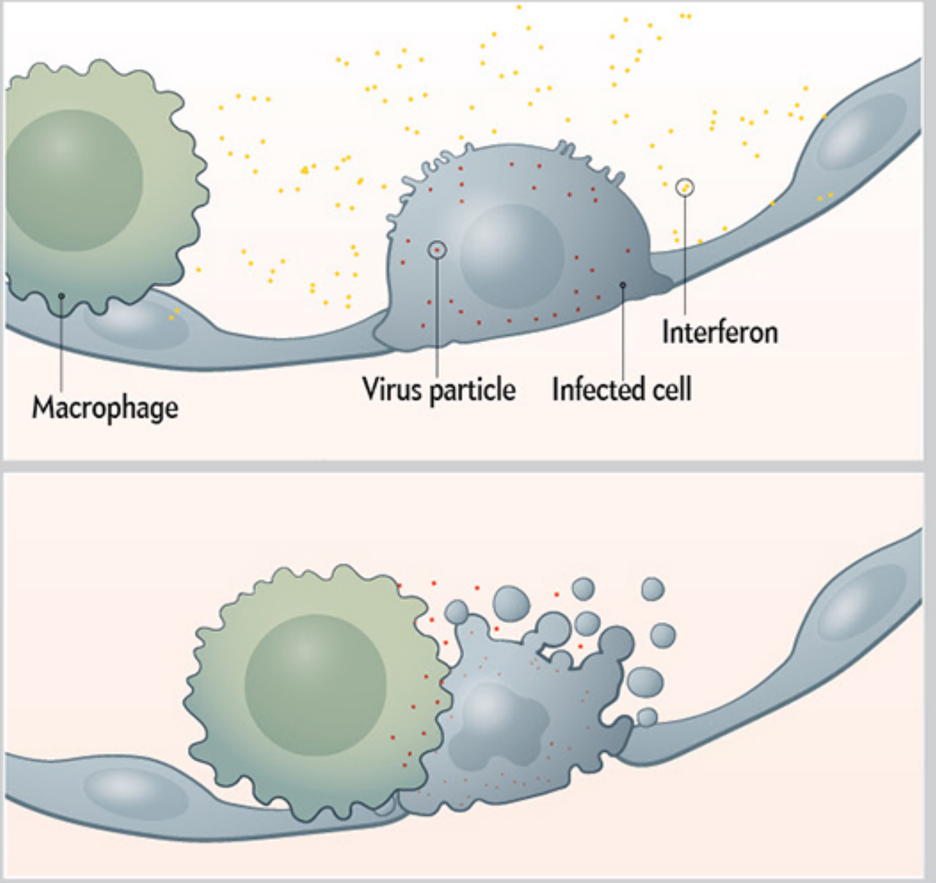
Coronavirus

Elapsed Time - 11 days

5 IMMUNE SYSTEM DEFENSE MEASURES

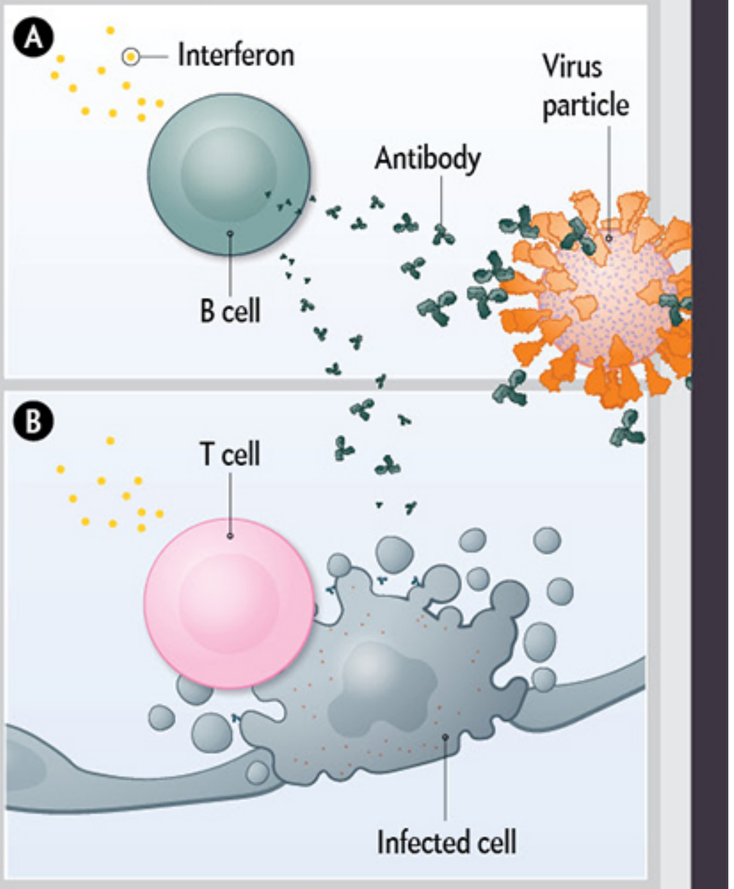
When infection begins, the innate immune system tries to immediately protect lung cells. The adaptive immune system gears up for a greater response.

INNATE IMMUNE SYSTEM: An infected cell releases interferon proteins that alert neighboring cells to create molecules that try to stop virus particles from entering or reproducing. Interferon also beckons cells such as macrophages in the bloodstream that can engulf virus particles.



TIME ELAPSED: 0–3 DAYS

ADAPTIVE IMMUNE SYSTEM: Interferon also alerts B cells. They produce "neutralizing antibodies" that might recognize parts of the spike protein and bind to it (A), preventing the spike from grabbing onto a lung cell. Interferon also recruits T cells, which can destroy viruses and also kill infected cells before viruses inside them burst out (B). Some B and T cells become memory cells that can quickly identify and fight a future invasion by the virus.



TIME ELAPSED: 6–11 DAYS

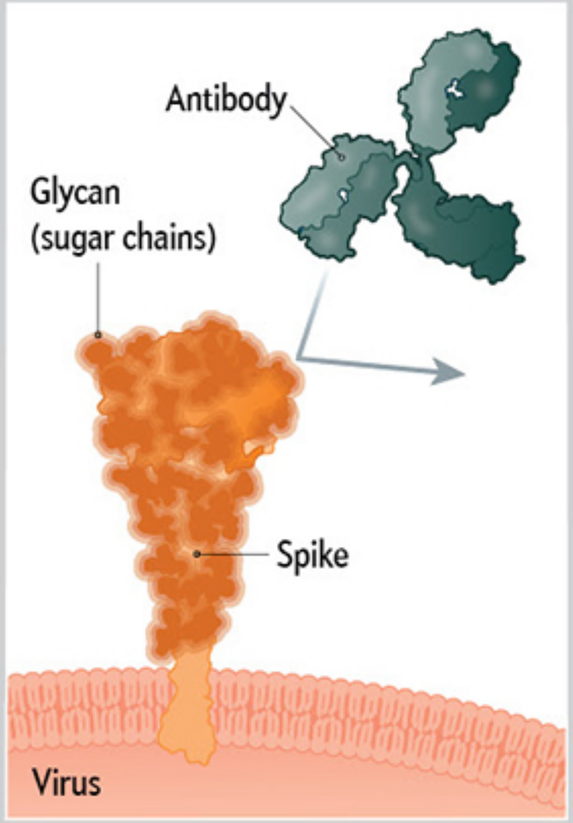
Coronavirus

Countermeasures

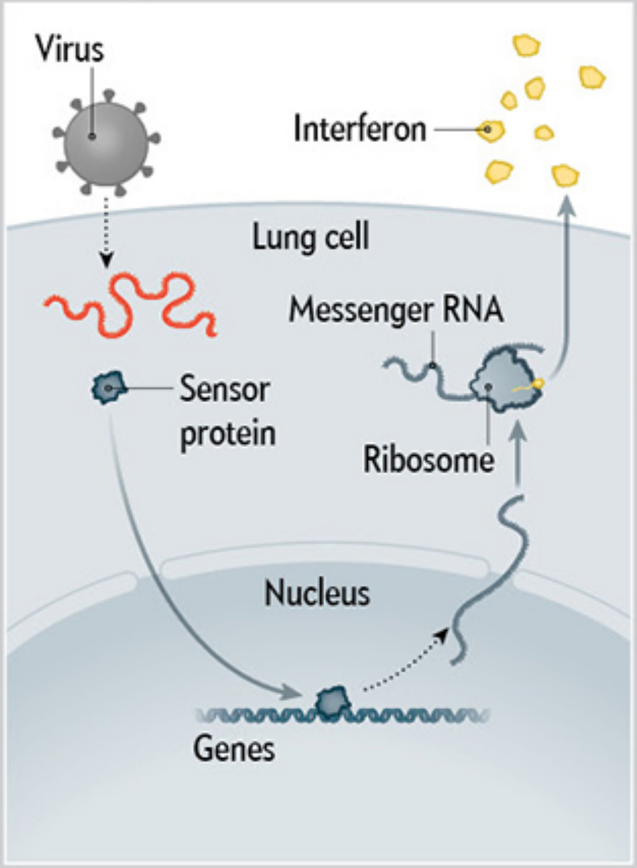
6 VIRUS COUNTERMEASURES

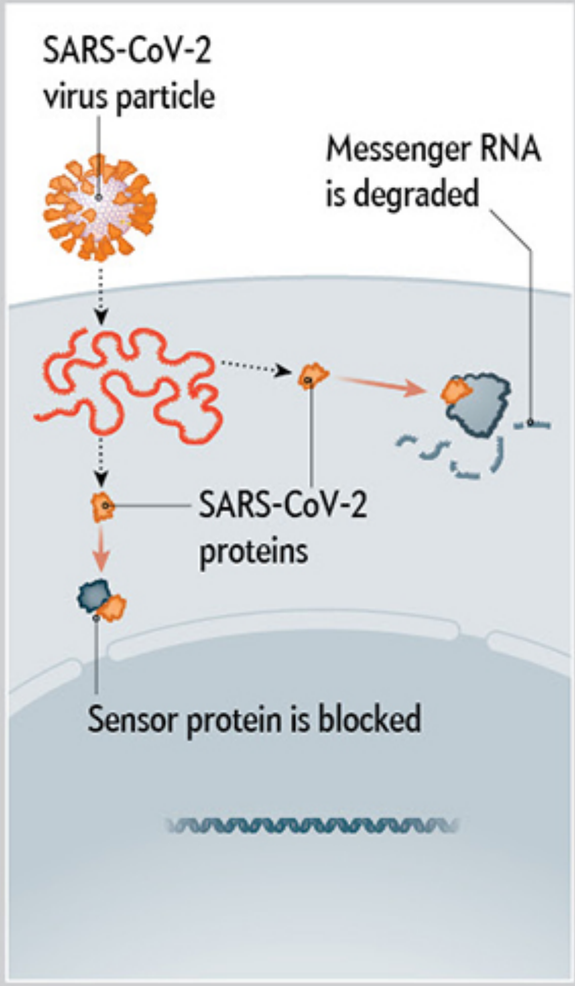
SARS-CoV-2 uses several tactics to thwart the immune system's response.

The virus spike may camouflage itself with sugar molecules. They flex and swing, potentially blocking antibodies from attaching to the virus, neutralizing it.



Normally, sensor proteins recognize incoming viruses as foreign and tell the cell nucleus to turn on genes for making messenger RNA molecules. The molecules deliver instructions to ribosomes to make interferon proteins that exit the cell to alert immune system cells ...



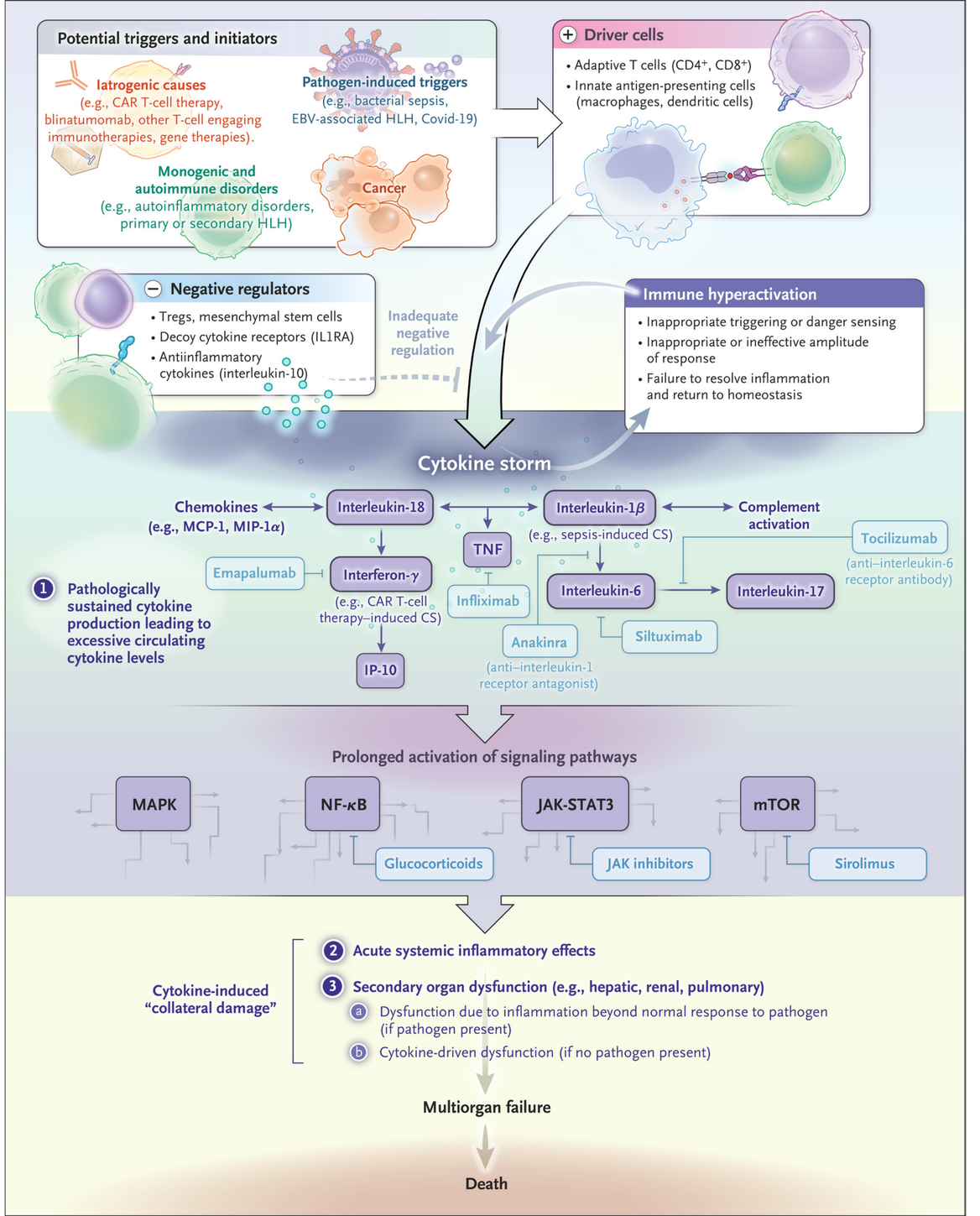


... Several SARS-CoV-2 proteins are thought to block sensor proteins from acting or to interfere with instructions to the ribosome.

Coronavirus

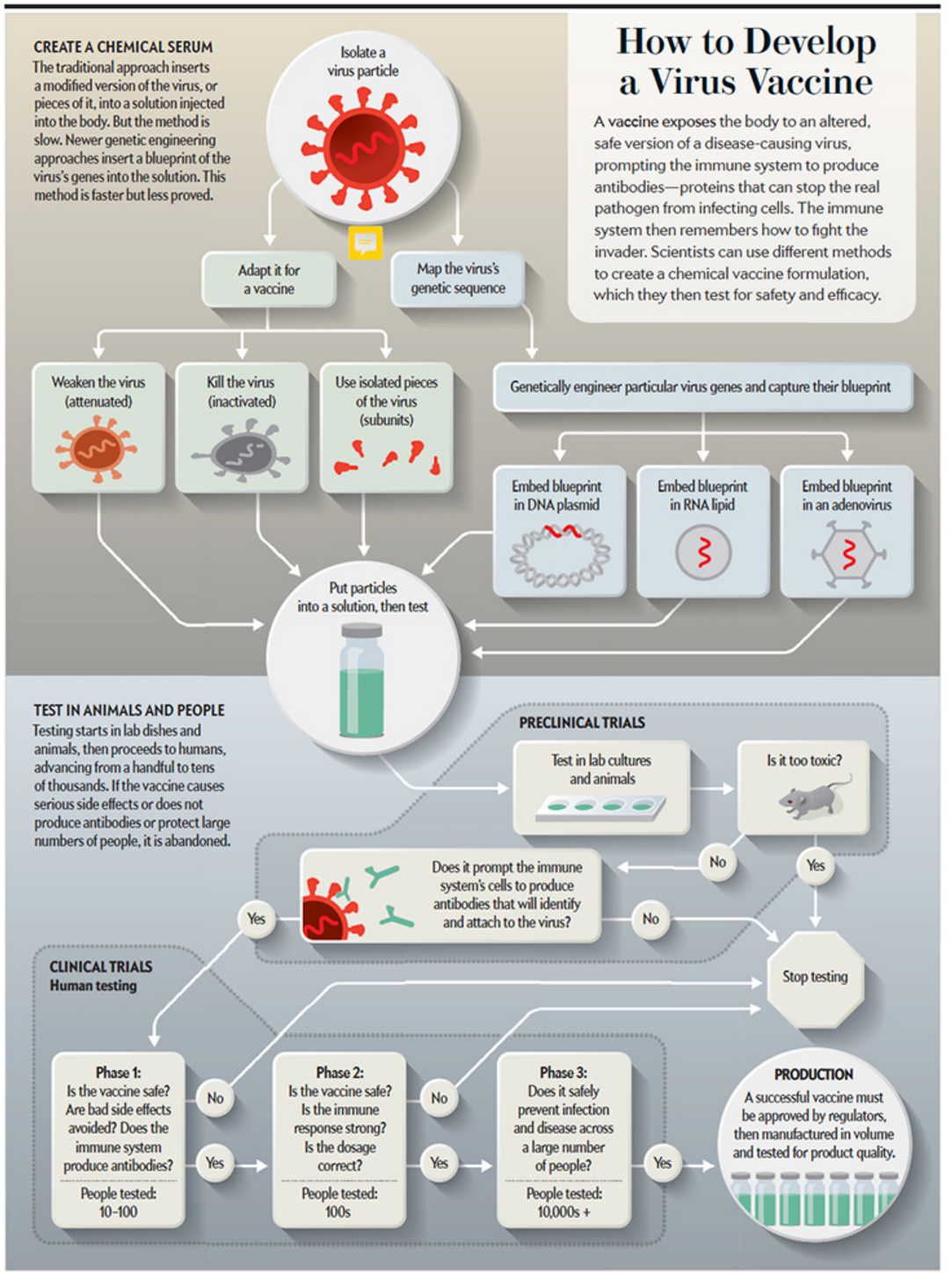
Cytokine Storm

Figure 2. Pathophysiological Features of Cytokine Storm.
Cytokine storm can occur as a result of inappropriate recognition (e.g., in hypersensitivity) or ineffective recognition with immune evasion (e.g., in Epstein–Barr virus [EBV]–associated hemophagocytic lymphohistiocytosis [HLH]), an inappropriate response with an exaggerated effector response and cytokine production (e.g., in chimeric antigen receptor [CAR] T-cell therapy) or an ineffective response due to immune evasion (e.g., in sepsis), or failure to terminate homeostasis or return to homeostasis (e.g., in HLH). Examples of drugs that can inhibit signaling pathways are shown in boxes. Covid-19 denotes coronavirus disease 2019, CS cytokine storm, IL1RA interleukin-1–receptor antagonist, IP-10 interferon-inducible protein 10, JAK-STAT3 Janus kinase–signal transducer and activator of transcription 3, MAPK mitogen-activated protein kinase, MCP-1 monocyte chemotactic protein 1, MIP-1α macrophage inflammatory protein 1α, mTOR mammalian target of rapamycin, NF-κB nuclear factor κB, TNF tumor necrosis factor, and Tregs regulatory T cells.



Coronavirus

Vaccine Development




That's all Folks!