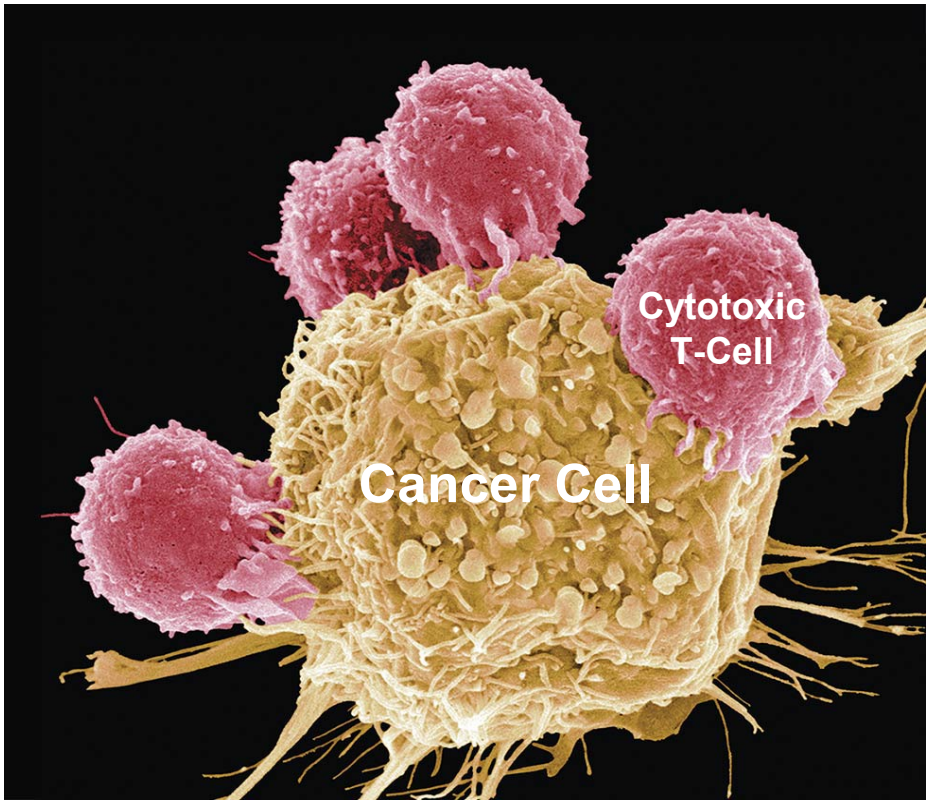
C21.5

The Third Line of Defense

"Acquired Immunity"

(Also Called "Adaptive Immunity")



What is immunity?

- *Immunity protects us against internal and external threats.*
- *Immunity may be either innate or acquired (also called adaptive)*
- *Innate immunity exists at time of birth // Relies on numerous factors including physical barriers, cellular phagocytes and many different types of molecules*
- *Innate immunity is characterized as being "non-specific resistance " with general characteristics (plasma molecules) shared by many different pathogens*
- *Acquired or Adaptive (Non-innate) Immunity means it does not exist at birth /// develops after birth /// characterized by "specificity and memory"*
- *We fight infections by using three lines of defenses:*
  - *#1 - Physical barriers*
  - *#2 - Non-specific resistance*
  - *#3 - Acquired immunity*

(both innate)

(not innate also called adaptive immunity)

The dual nature of the adaptive immune system.

humoral

Humoral (antibody-mediated) immune system
Control of freely circulating pathogens

Extracellular antigens

1 A B cell binds to the antigen for which it is specific. A T-dependent B cell requires cooperation with a T helper (T_H) cell.

B cell

2 The B cell, often with stimulation by cytokines from a T_H cell, differentiates into a plasma cell. Some B cells become memory cells.

Plasma cell

3 Plasma cells proliferate and produce antibodies against the antigen.

cellular

Cellular (cell-mediated) immune system
Control of intracellular pathogens

Intracellular antigens are expressed on the surface of an APC, a cell infected by a virus, a bacterium, or a parasite.

T cell

1 A T cell binds to MHC–antigen complexes on the surface of the infected cell, activating the T cell (with its cytokine receptors).

Cytokines activate T helper (T_H) cell.

Cytokines activate macrophage.

Cytokines

Cytokines

Cytokines from the T_H cell transform B cells into antibody-producing plasma cells.

T_H cell

2 Activation of macrophage (enhanced phagocytic activity).

Memory cell

Cytotoxic T lymphocyte

3 The CD8⁺T cell becomes a cytotoxic T lymphocyte (CTL) able to induce apoptosis of the target cell.

Some T and B cells differentiate into memory cells that respond rapidly to any secondary encounter with an antigen.

Lysed target cell

KEYCONCEPTS

- The adaptive immune system is divided into two parts, each responsible for dealing with pathogens in different ways. These two systems function interdependently to keep the body free of pathogens.
- **Humoral immunity**, also called antibody-mediated immunity, is directed at freely circulating pathogens and depends on B cells.
- **Cellular immunity**, also called cell-mediated immunity, depends on T cells to eliminate intracellular pathogens, reject foreign tissue recognized as nonself, and destroy tumor cells.

How is acquired immunity managed?

T-cells and B-cells are the key cells responsible for acquired immunity /// these cells must first be born, educated, deployed /// after being deployed these cells will "rest" until a pathogen enters the body // this will cause the T and B cells to enter their last phase: recognize, react, remember

Born = place where T and B cells are formed (created)

Educated = this occurs when T and B cells receive "unique receptors" matched to billions of different possible foreign antigens

Deployed = after receiving their receptors, they are called naive immunocompetent T and B cells and are released into the blood. These cells are free to wander anywhere throughout the body but many rest in the lymph nodes /// The next step occurs when pathogen enters the tissue > the three "R"s.

Recognize = naive immunocompetent T and B cells are not able to "see the pathogen" until after an antigen presenting cells "shows" the T and B cells the pathogen now invading the Body // these cells are no longer naive but are now "turned on"

React = where "turned on" cytotoxic T cells (C-Tc) and helper T cells (H-Tc) eliminate threat From pathogen

Remember = making memory T and B cells to be used in next exposure to same pathogen

Outline for the function of acquired immunity.

All formed elements made in red bone marrow

Born

Educated

Deployed

(Deployed as naive immunocompetent cells)

ACTIVATE To

Recognize

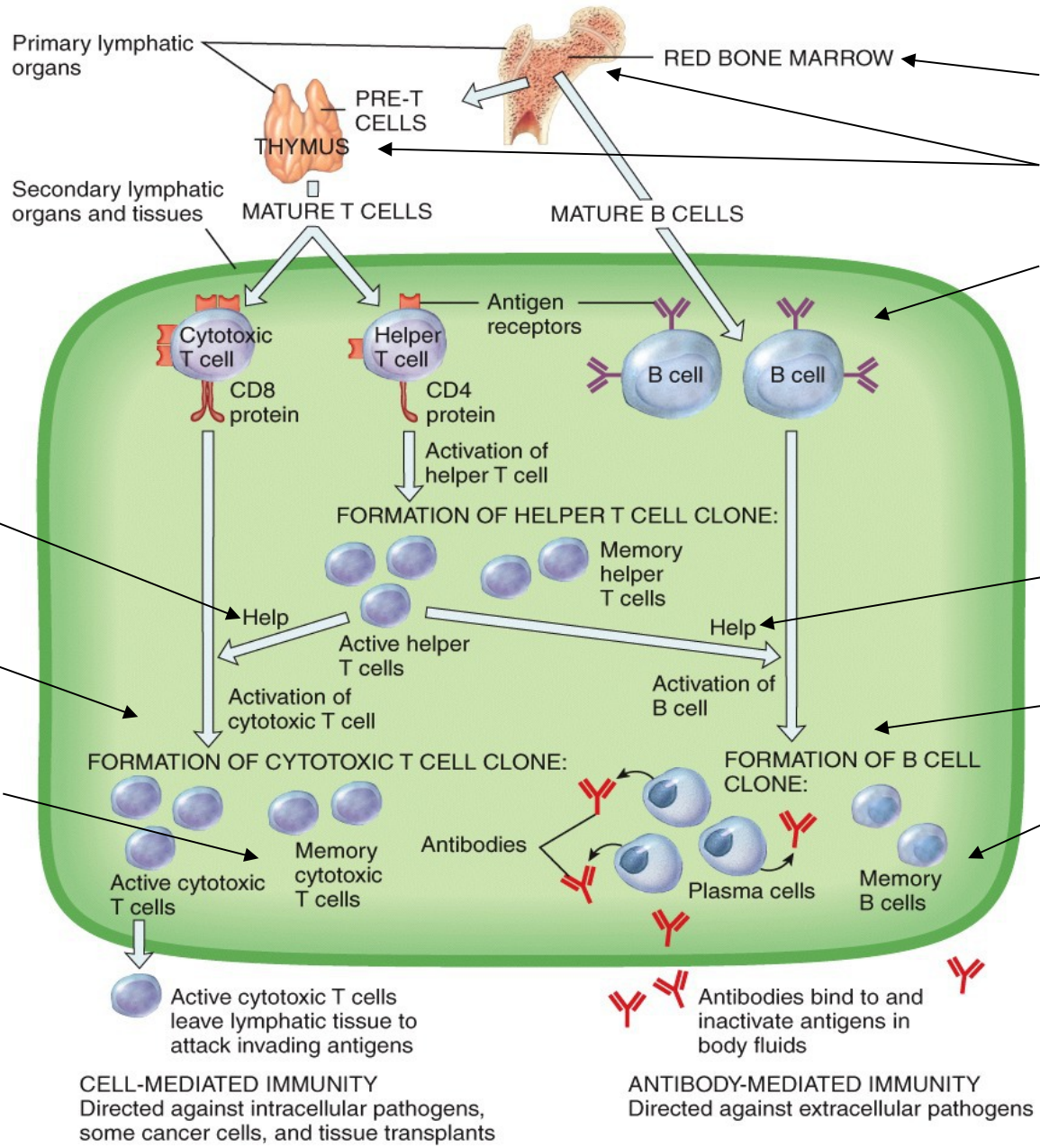
React

Remember

Recognize

React

Remember



What makes acquired immunity so special?

Two important characteristics = "specificity and memory"

Acquired immunity recognizes the pathogen because it has "non-self antigen"

Acquired immunity uses many other WBC to support and coordinate the activities of T and B cells

All these WBC must work together (i.e. talk to each other)

WBC use cytokines and chemokines to communicate with each other

There is also cooperation between innate and non-innate immunity and this is also mediated by cytokines

What Are the Two Forms of Acquired Immunity?

- *WBCs called T cells provide cellular adaptive immunity // Cytotoxic T cells - kill host's cells infected with bacteria.*

- *WBCs called B cells (when activated they change into plasma cells) provide humoral adaptive immunity /// After B cells morph into plasma cells they produce antibodies /// antibodies do not kill pathogens /// antibodies render pathogens* harmless and tag them for destruction.

- *Clonal selection occurs after T and B cells are activated APC /// results in rapid mitosis of T and B cell // each cell type have similar receptors matched to a specific foreign antigen on a specific pathogen*

- *Cytotoxic -Tcell, helper-Tcell, and B cells will all have similar receptors able to dock onto the same pathogen's foreign antigen /// during clonal selection memory cells are made to similar antigen but rest in lymph nodes f*

- *Memory cells do not react to "current infection" but will respond immediately after a second exposure to similar pathogen. /// first exposure vs second exposure*

Why do we need cellular and humoral immunity?

Because the pathogen can be either outside or inside our cells!

Humoral Adaptive Immunity: B cell morph into plasma cells after activated // plasma cells make antibodies /// antibodies only attack antigens when they are outside our cells.

Cellular Adaptive Immunity: Cytotoxic T cells (i.e. cellular immunity) recognize foreign antigen when they are "hiding" inside our cells.

Therefore, when we are infected by a bacteria, our acquired immune system must activate both T cells and B Cells. These cells have receptors matched to the same foreign antigen!

Each cell line (T and B) have receptors that are able to recognize the same foreign antigen /// waiting in our lymph nodes are "billions" of naive immunocompetent T and B cells just waiting to become activated /// each pair of cells will have a unique receoptor

Note: When T and B cells are educated "each B and T cell pair" will receive just one out of a possible billion different foreign antigen receptors. This means we have billions of "B cells and billions of T cell forming pairs" that share a common foreign antigen receptor unique to a pathogen's antigen.

Key Factoids

Immune system differentiate between self and non-self antigens

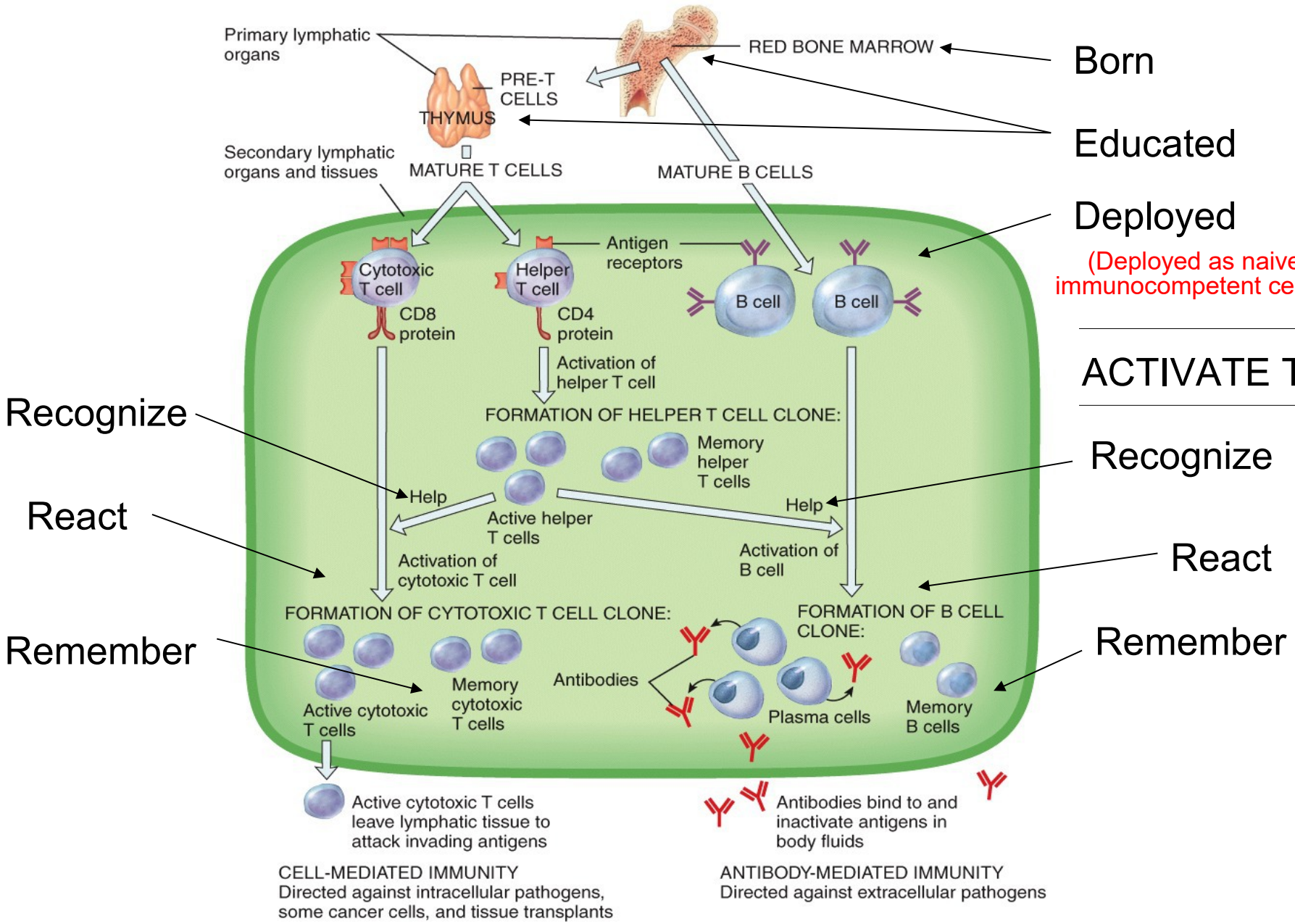
Immune system function is to eliminate pathogens

Cytotoxic T cells are able to kill infected host cells

Use antibodies to render pathogen harmless and tag pathogen for destruction /// this occurs in body fluids // antibodies made by plasma cells

Another lymphocyte called Natural Killer Cells (NK cell) are able to kill infected host cells but uses a different types of receptors // evolved to kill host cells infected by cancer or virus /// KN cells do not require MHCP activation pathway // NK cells perform immune surveillance

Outline for the structure and function of acquired immunity.

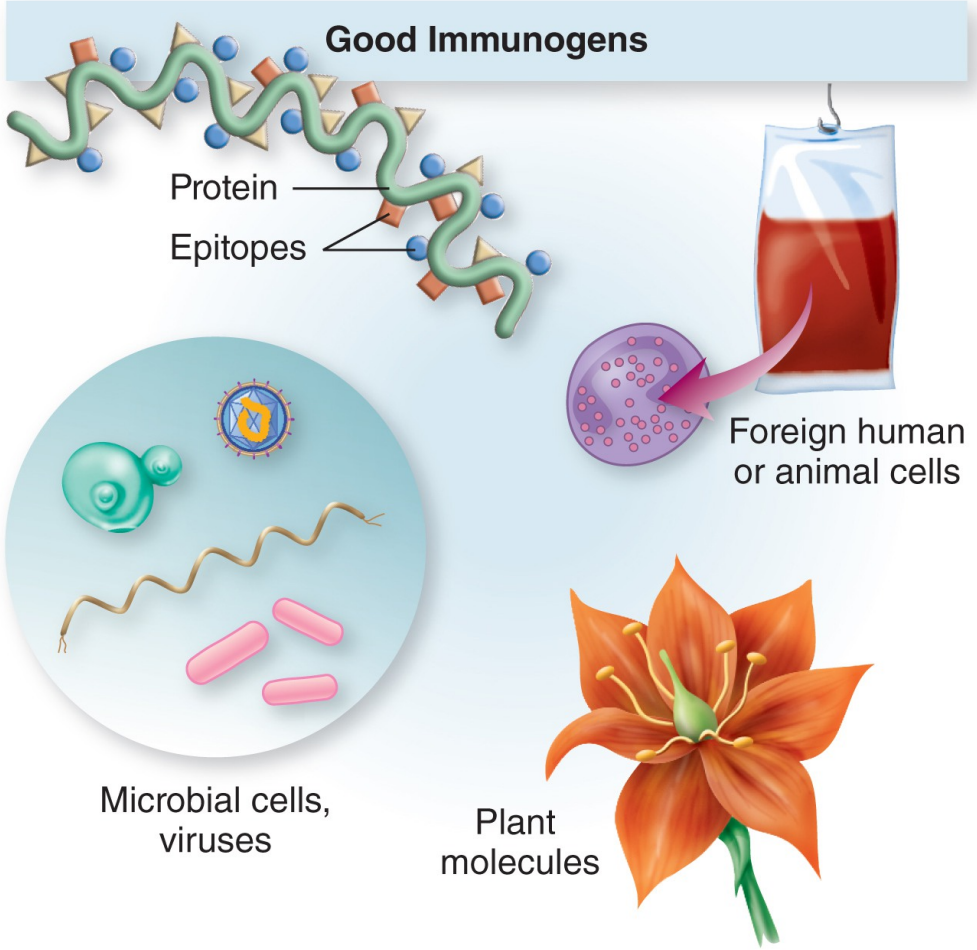


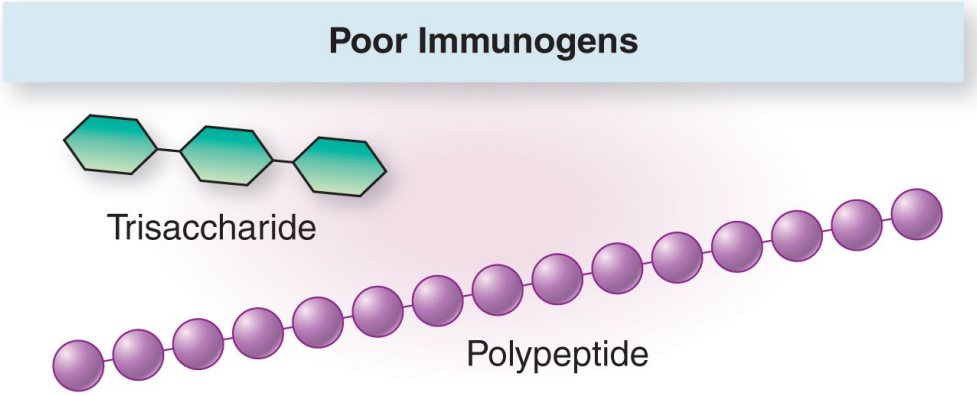
After T Lymphocytes are “Educated” Each T Cell Has a Unique Receptor

Deployed as “Naïve Immunocompatent” T Lymphocytes (helpers and cytotoxic)

Naïve Immunocompatent T Cells Receptors Bind to MHCP-Epitope Complex (antigen segment) to Initiates Clonal Selection

Clonal selection results in mitosis where millions of similar cells are formed. All activated with similar receptors.

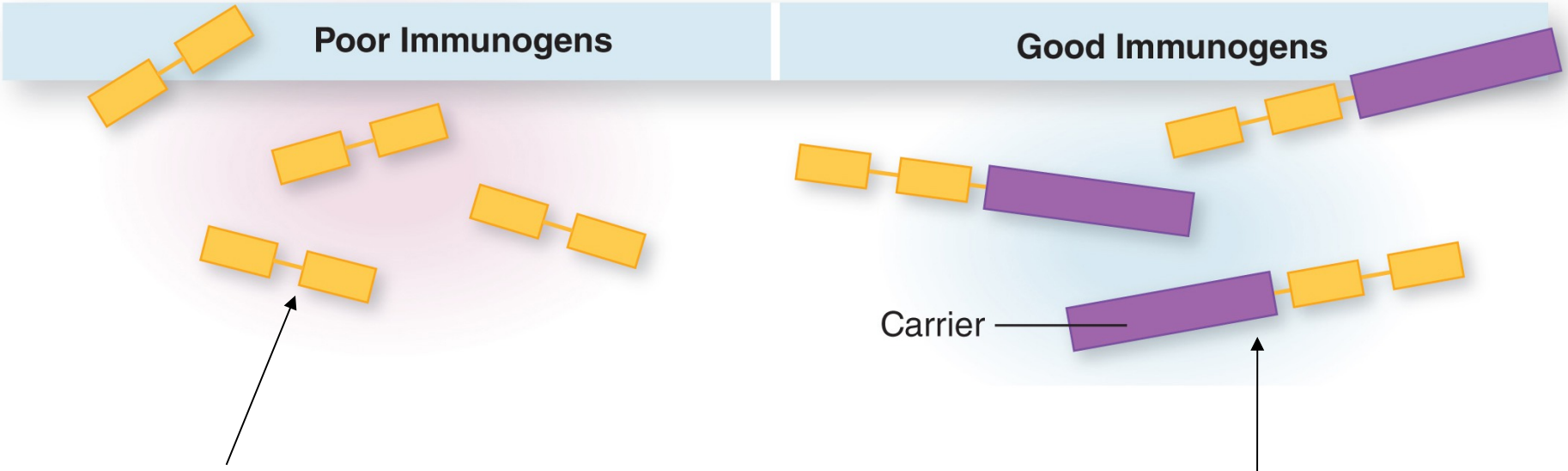




Foreign antigens (i.e. non-self antigens) are also known as immunogens!

Antigens are large molecules.

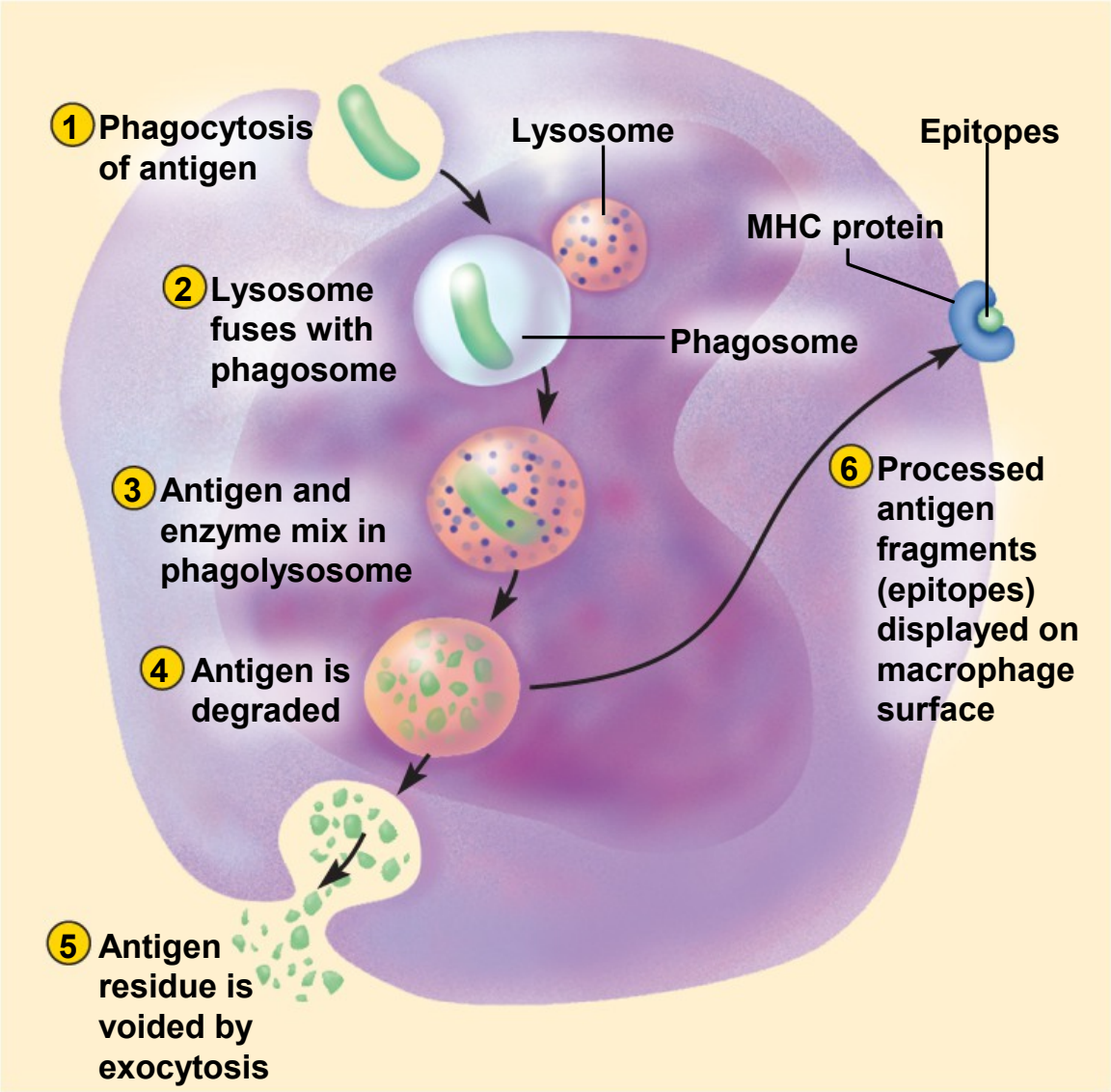
Haptens



Haptens are too small to act as an antigen.

After haptens joined to a “carrier” (e.g. albumin) they can now be recognized as an antigen.

How Do Antigen Processing Cells Turn Antigens into Epitope and then Display Epitope on Outer Surface of the Plasma Membrane?



MHC protein hold the epitope and may be either type-I or type-II

Macrophage and B cells have MHCP-II // both are APCs

Dendritic cells = APC //// MHCP Class-I and Class II

T Cell have “receptors” that bind to either type I or type II MHCP

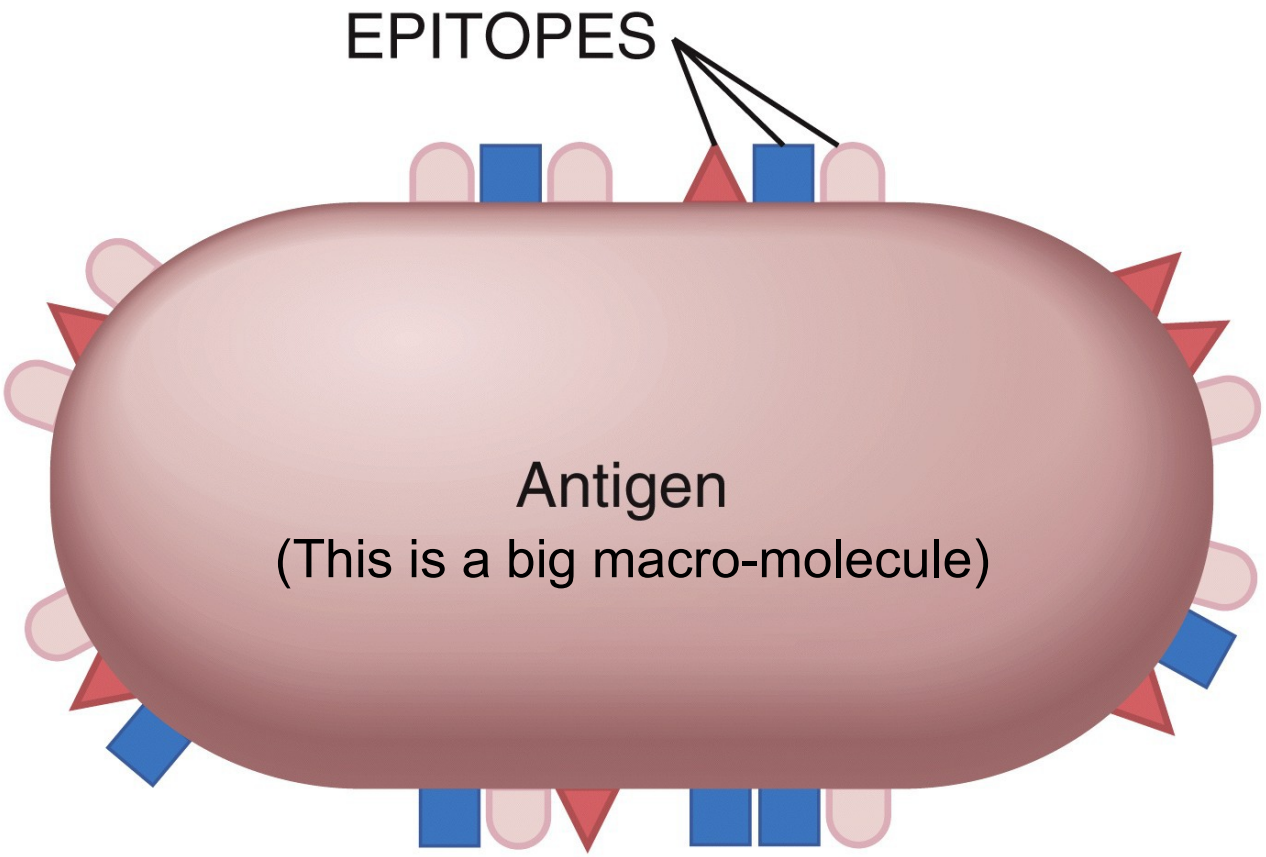
Helper T-cells receptors only bind to MHC-II // must occur to activate H-Tc

Cytotoxic-T-cells receptors only bind to MHC-I // must occur to activate C-Tc

NK cells receptors use different clusters of differentiation to recognize virus or cancer // when NK engage with markers take 3 days to reach peak activity

All nucleated host cells have only MHC-I

A single antigen molecule may generate many epitopes. The proteosome will degrade the antigen and create protein fragments that are processed by the endoplasmic reticulum. The endoplasmic reticulum put epitopes into vesicles that are then inserted into the host's plasma membrane.



Major Histocompatability Proteins
(MHCP-1 VS MHCP-2)

Cells use proteosomes to degrade cytoplasmic proteins into fragments // foreign cell's protein fragments (called epitopes) are displayed on the outer surface of the plasma membrane in MHCP which maybe type-I or type-II (the epitopes are like the pathogens “finger prints”)

Cytoplasmic proteins fragments displayed by host cells maybe ”normal” host cell proteins (endogenous) or from unusual proteins associated with cancer, bacteria, or virus. /// Host cells only have MHCP-1 /// Protein fragments are picked up by MHCP-1 and inserted on the outer surface of the host's plasma membrane

Now we know what cells are infected (if they have epitopes). The next step is to activate naive immunocompetent C-Tc and naive immunocompetent H-Tc with receptors matched to the epitopes of infected host cells.

This will require antigen presenting cells (APC). These cells help naive T and H cells (specific naive immune cells with receptors only able to bind to the displayed epitope) recognize the pathogen inside our cells.

C-Tc cells have receptors only able to dock with MHCP-I and H-Tc cells have receptors only able to dock with MHCP-II (now it becomes confusing so keep the type I and type II separate).

Major Histocompatability Proteins
(MHCP-1 VS MHCP-2)

APC (macrophage and dendritic cells) capture the bacteria infecting our cells, process the epitopes, then deliver this info to the lymph nodes

Macrophage use MHCP-II so naive Th cells with matching receptor to the displayed epitope may dock to macrophage to activate naive Th cells

Dendritic cells use MHCP-I and MHCP-II so dendritic cells may activate both Tc or Th cells with appropriate receptor to dock to the APC dendritic cell.

Now we have activated both Tc and Th cells which have specific receptors match to the bacteria that is infecting the host cell. Tc receptors now may engage directly with the infected host cells.

The Th secretes cytokines are required to finalize the activation of the Tc cell.

Fully activated CTc receptor now may dock to the host cell MHCP-I-epitope and kills the cell with the kiss of death // CTc cell then undocks and goes to next infected cell and kills it. After all infected host cells killed, this group of CTc dies by apoptosis.

Major Histocompatability Proteins (MHCP-1 VS MHCP-2)

B cells provide humoral immunity. B cells function as their own APC.

If naive immunocompetent B cell's receptor engages with a bacteria's antigen, the B cells engulfs the bacteria and processes its epitope. // use MHCP-II to display bacteria's epitope on B cell plasma membrane // at this point the B cell is only partially (weakly) activated and produce some plasma cells making few antibodies and no memory cells

If activated H-Tc recognize B cell epitope then H-Tc secretes cytokines and the B cell becomes fully activated - makes many more antibodies as well as memory B cells // more on this topic later

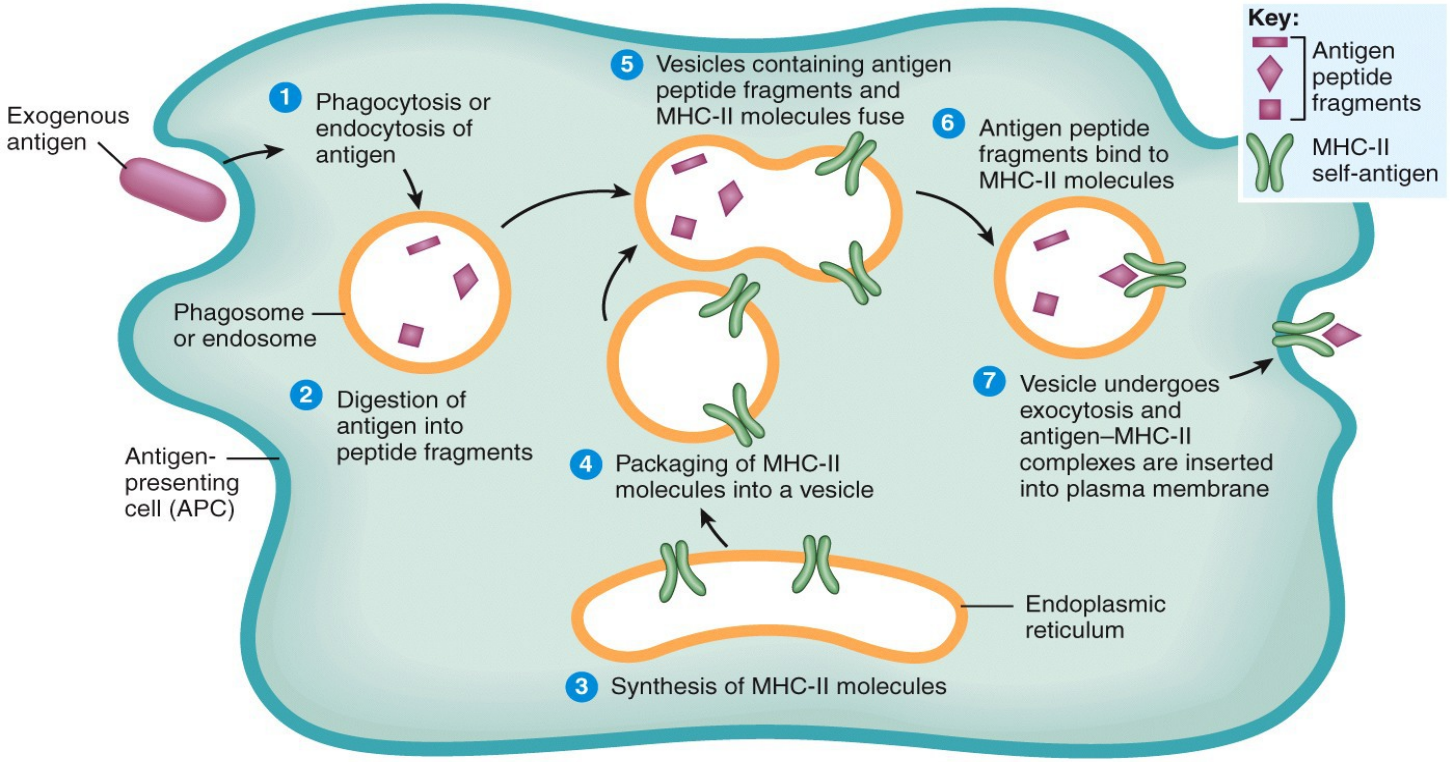
The activated B cell morphs into plasma cell to make antibodies // these molecules neutralize bacteria outside of our cells by rendering the bacteria harmless and tag them for destruction. Compliment will destroy the tagged pathogen.

NK cells receptors use different clusters of differentiation to recognize virus or cancer // after NK engage with host cells epitope it will take 3 days to reach peak activity

In conclusion, immunity is complicated! /// more slides to illustrate these steps.

Antigen Processed Cells Using MHC-II

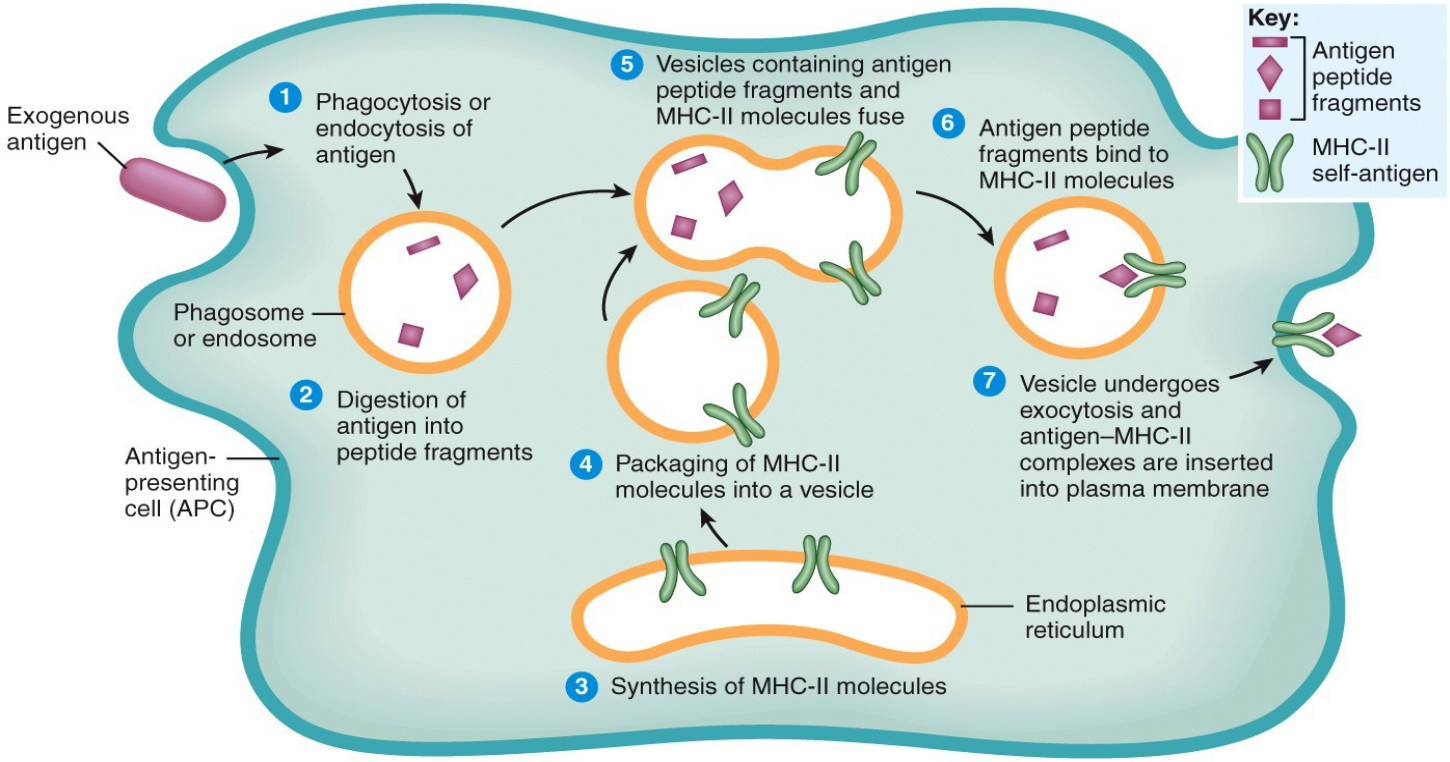
Macrophage and dendritic cells are antigen processing cells that have MHC-II proteins. The APCs engulf exogenous antigen and present their epitope-MHC-II complex in the plasma membrane. Naïve immunocompetent helperTcells (CD4) with matched receptors bind to the MHC-II-complex. This activates the helper Tcell.



APCs present exogenous antigens in association with MHC-II molecules

Antigen Processed Using MHC-I by Dendritic APC

Dendritic cells are antigen processing cells that have MHC-I and MHC-II proteins. This means dendritic cells may activate both naive Tc as well as naive Th cells

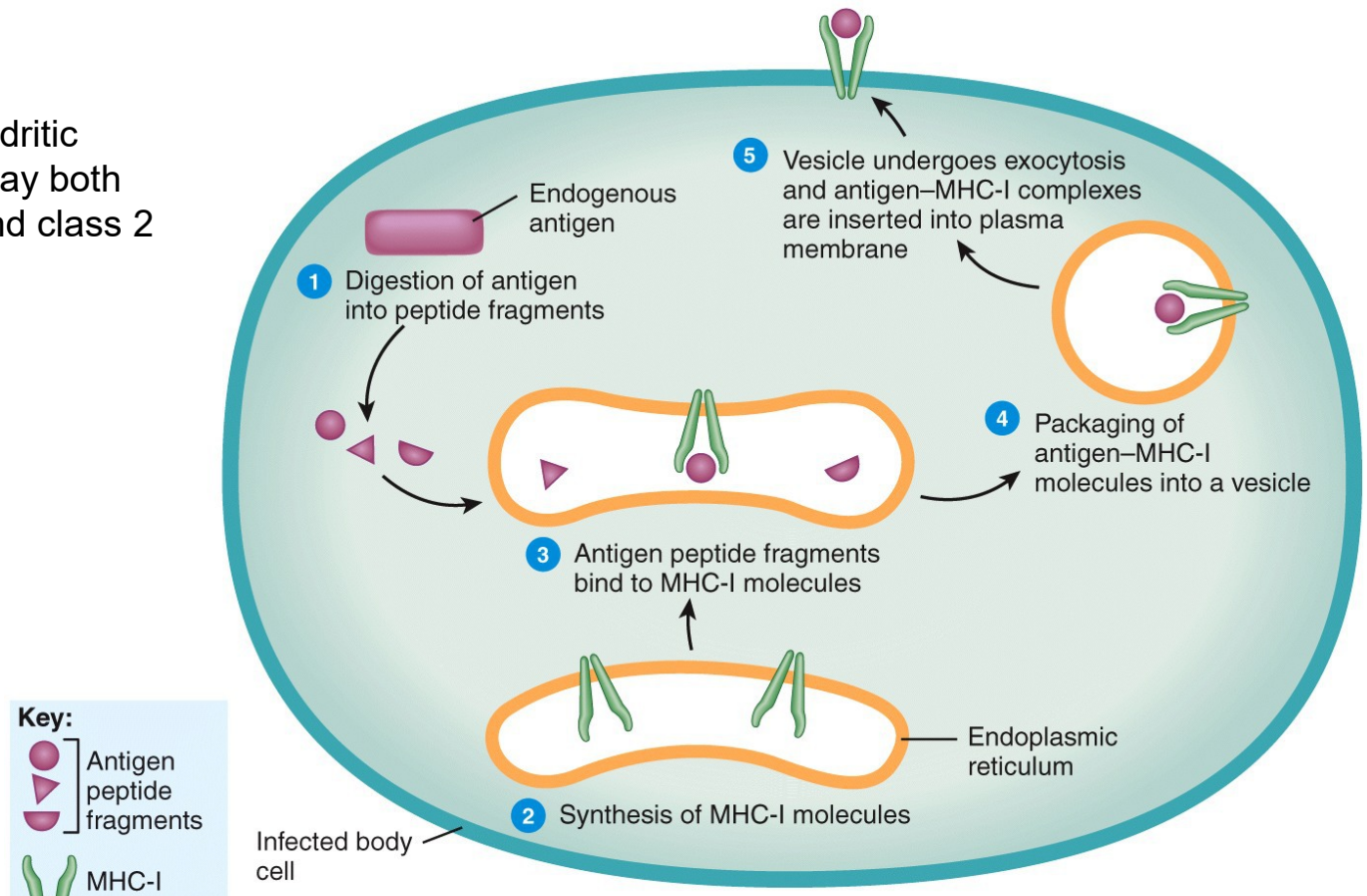


APCs present exogenous antigens in association with MHC-II molecules

How Host Cells Process and Display Foreign Antigen Using MHC-I

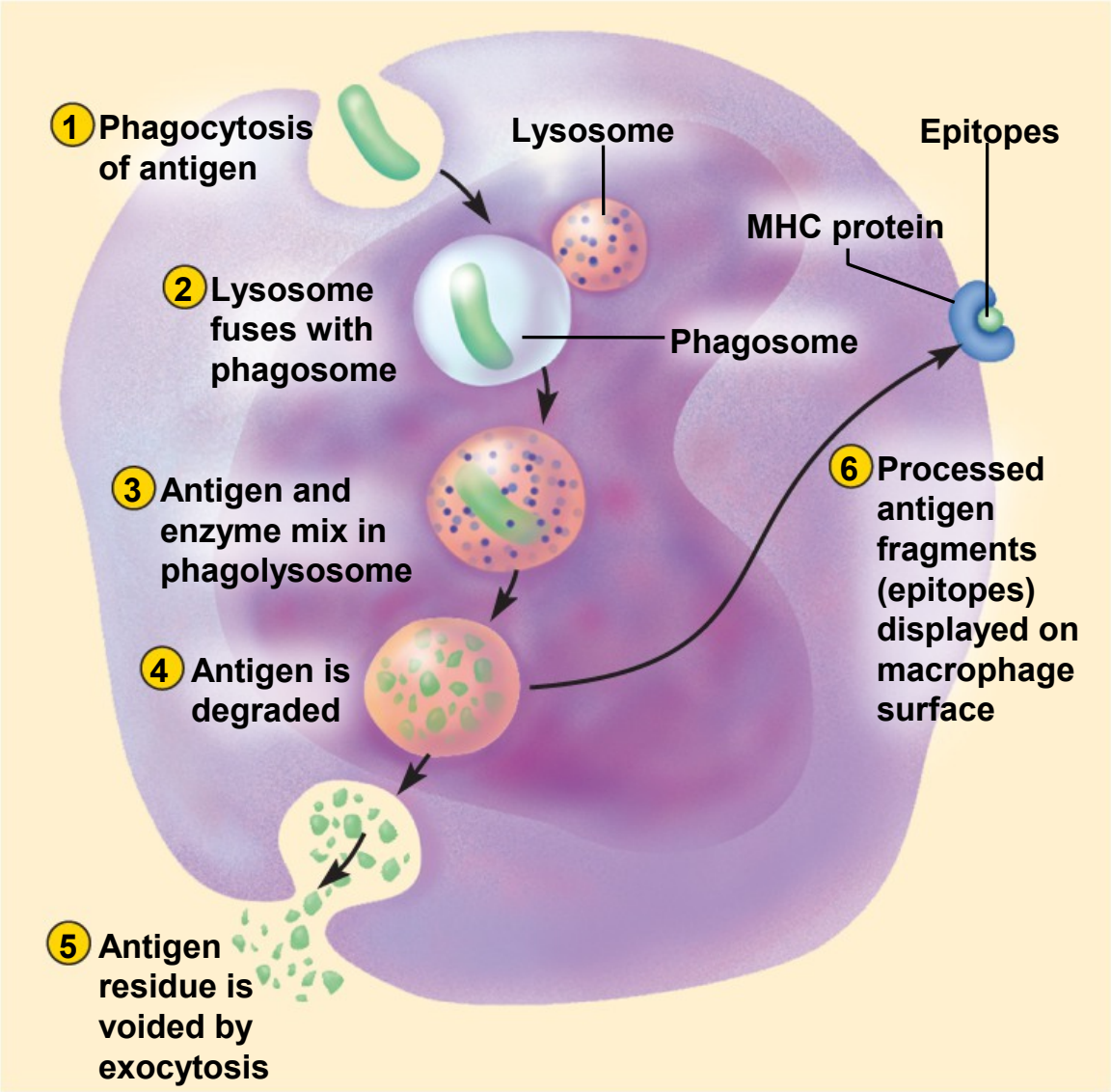
Placing epitope into the host cell's plasma membrane will allow activated cytotoxic T cell receptors to recognize infeced cells. If the cell displays bacterial epitope in MHC-I complex then cytotoxic T cell will form a c-T-cell-receptor-MHC-1 complex. Now the c-T-cell kills the infected cell with the “kiss of death”. Endogenous implies that the proteins are from the cell's cytoplasm. // Only cytotoxic T cell receptors recognize MHC-I type molecules.

Note: dendritic cells display both class 1 and class 2 MHCP.



Infected body cells present endogenous antigens in association with MHC-I molecules

How Do Antigen Processing Cells Turn Antigens into Epitope and then Display Epitope on Outer Surface of the Plasma Membrane?



MHC protein may be either type-I or type-II

Macrophage and B cells have MHCP-II // both are APCs

Dendritic cells = APC and have both MHCP Class-I and Class II

Helper T-cells receptors only bind to MHC-II // must occur to activate H-Tc

Cytotoxic-T-cells receptors only bind to MHC-I // must occur to activate C-Tc // Dendritic cell activate C-Tc

NK cells receptors use different clusters of differentiation to recognize virus or cancer // when NK engage with markers take 3 days to reach peak activity

All nucleated host cells have only MHC-I

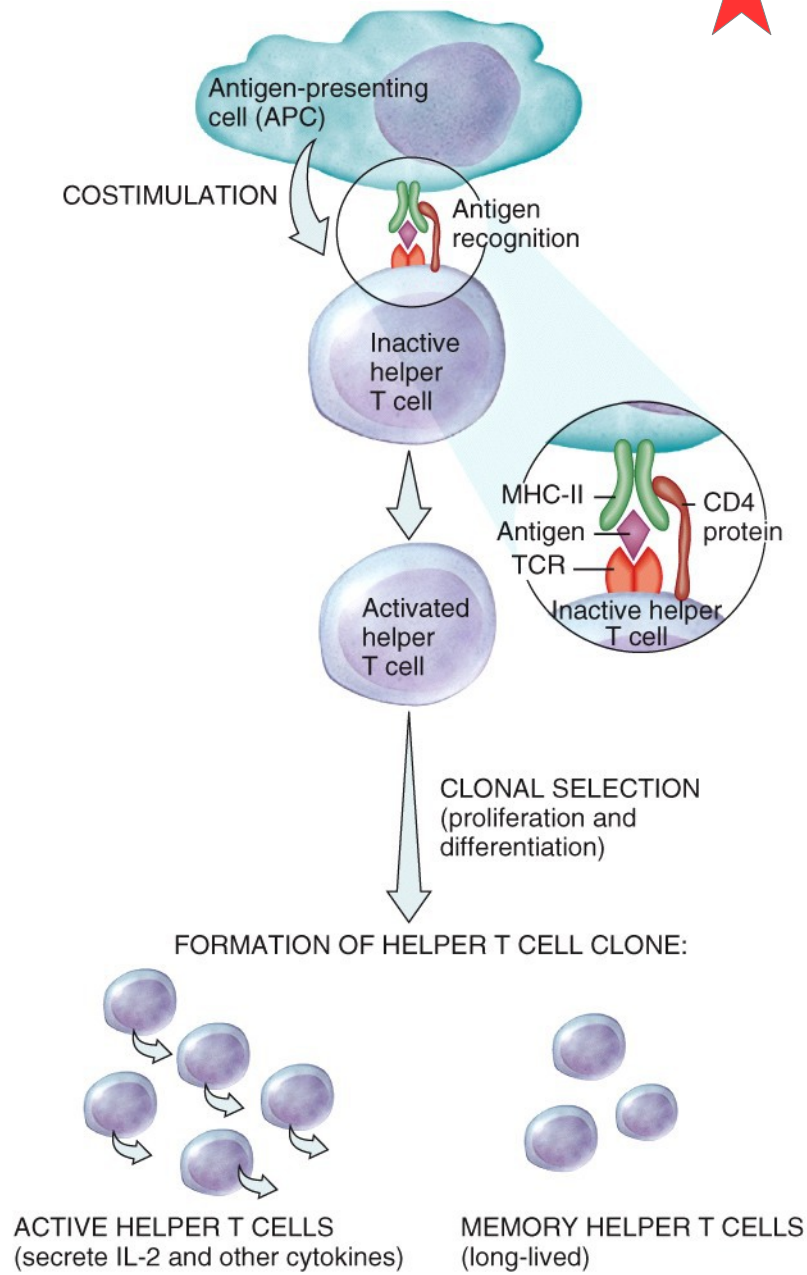
Activation of Helper T Cells

Immune system must activate helper T cells using Antigen Presentation Cells // HTc only have receptors for MHCP-II (APC maybe either Dendritic Cells or Macrophage)

Activated Helper T cell must secrete cytokines (interleukin 2) <u>to complete the activation of both cytotoxic T cells and B cells.</u>

Helper T cells will also attract to area of infection macrophage, NK cells, and other inflammation responses

Note: the CD4 protein on helper T Cell functions as a costimulatory factor in the activation of helper T Cell



How Are H-Tc Activated?

- Helper T Cells receptors bind to the epitope-MHC-II-complex of an antigen presenting cell (APC) /// e.g. macrophage or dendritic cell

- If APC is a macrophage, after the H-Tc binds to the macrophage then the macrophage secretes interleukin-1 (this then stimulates and activates H-Tc)

- Activated H-Tc responds by secreting interleukin-2 // interleukin-2 stimulates macrophage to secrete more inerleukin-1 /// this creates positive feedback loop /// macrophage continues to secretes more interleukin-1 /// ***this is a key step in the overall activation of acquired immunity***

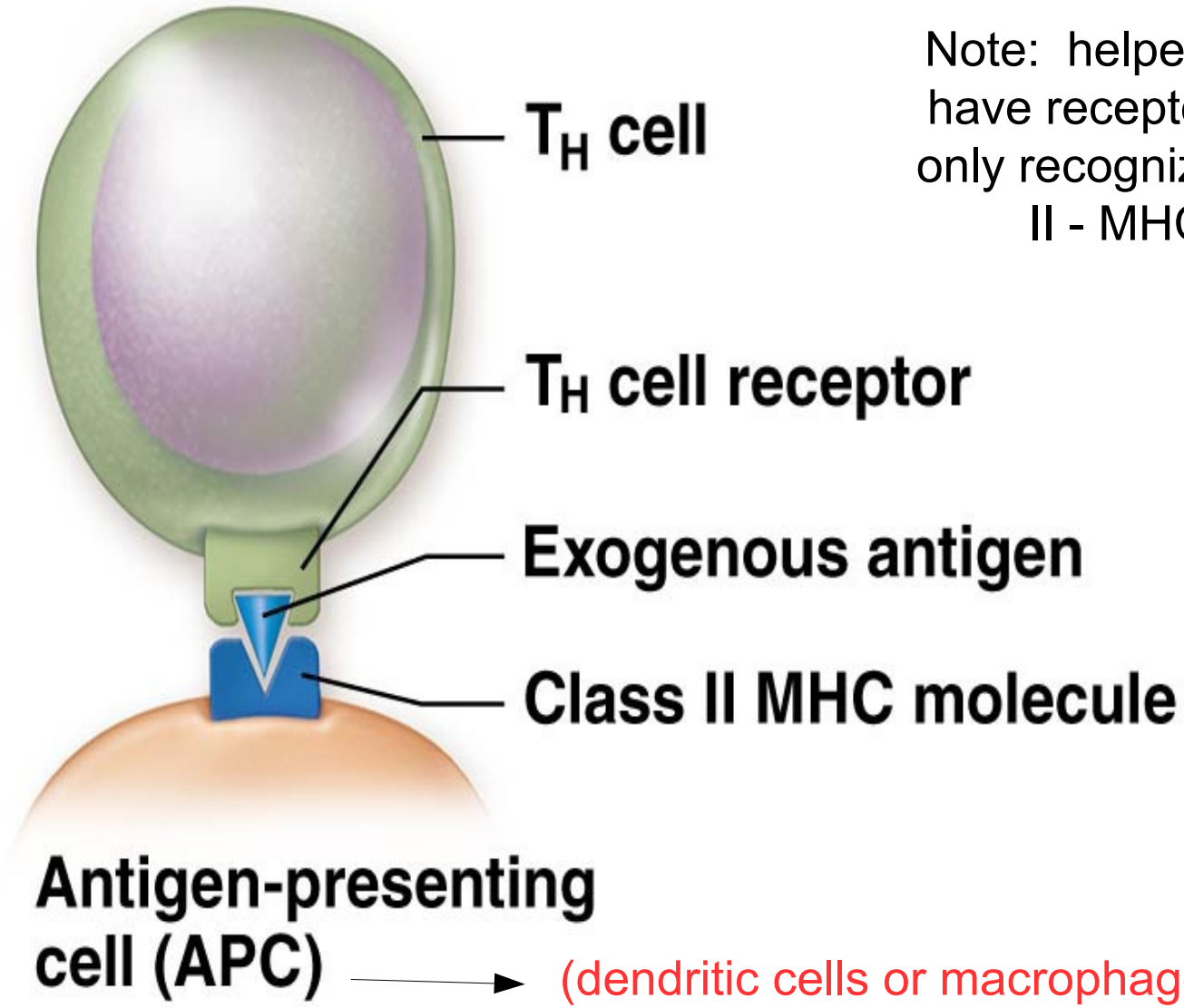
- Activated Helper T Cells now themselves undergoes clonal selection /// H-Tc continues to secrete interleukin-2 with following outcomes.....
  - Make many more similar (with same receptor type) active H-Tc
  - H-Tc cytokines are also required to complete activation of cytotoxic Tc
  - H-Tc cytokines are required to fully activate B-cells
  - Form memory H-T cells – saved and rest for future use
  - Form regulatory T cells – controls intensity of immune response

- Activated T Helper cells will also stimulate non-specific defenses /// stimulate more macrophage and NK cells to emigrate into the area and initiates inflammation

This is how a naive immunocompetent helper T cell is activated to initiate clonal selection.

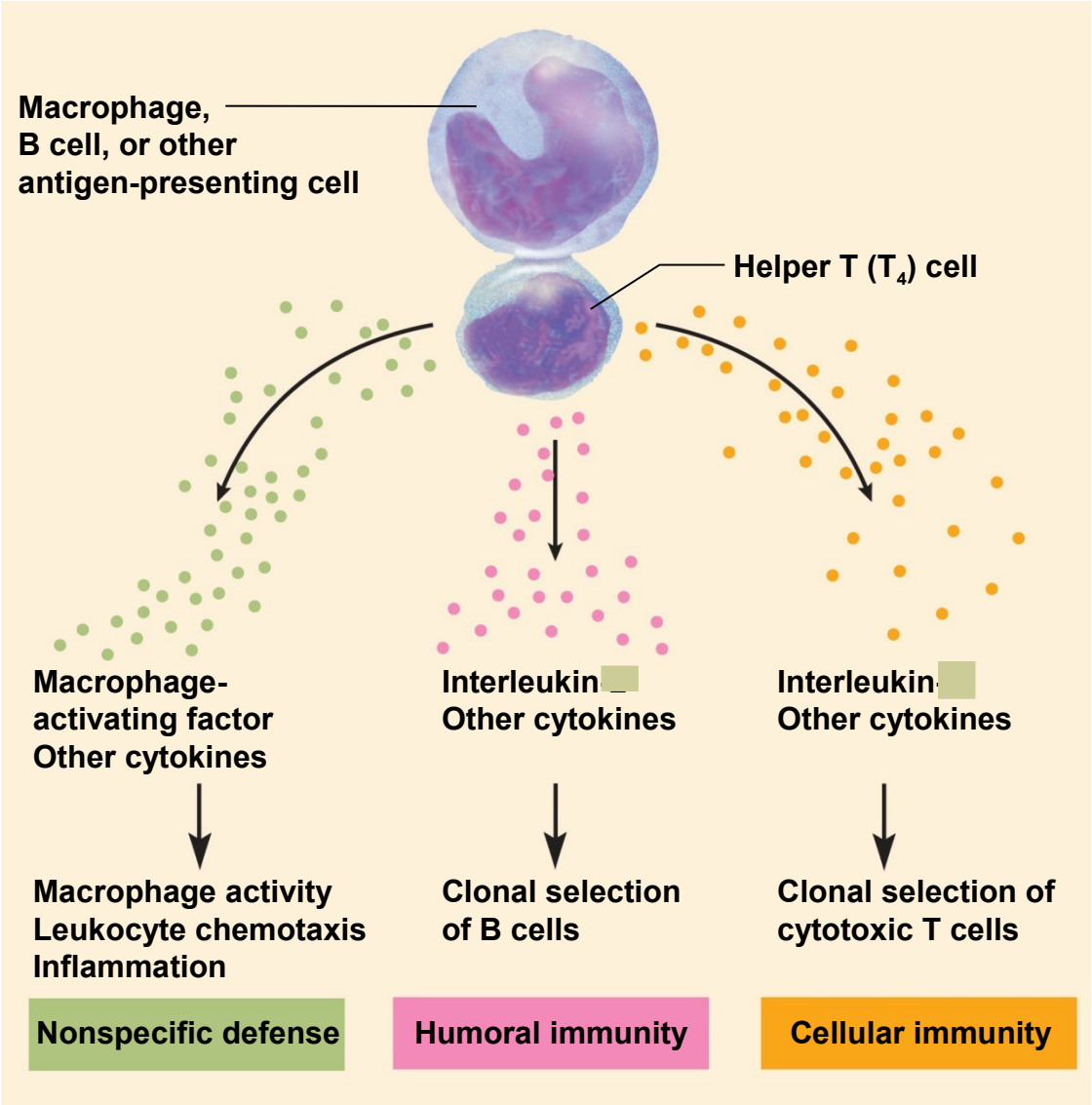
After activation this H-Tc will secrete cytokines to complete activation of both cellular immunity (C-Tc) and humoral immunity (H-Tc)

Note: helper-Tcells have receptors that only recognize class II - MHCP



(dendritic cells or macrophage display class-II)

Helper T Cell's
Perform a Pivotal Role in Three Forms of Immunology



T_H Cells are required to activate both humoral and cellular immunity

TH Cells release cytokines that increase the activity of macophage, leukocyte chemotaxis and inflammation.

Without activated H-T_C you will lack both the 2nd and 3rd line of defenses against pathogens!

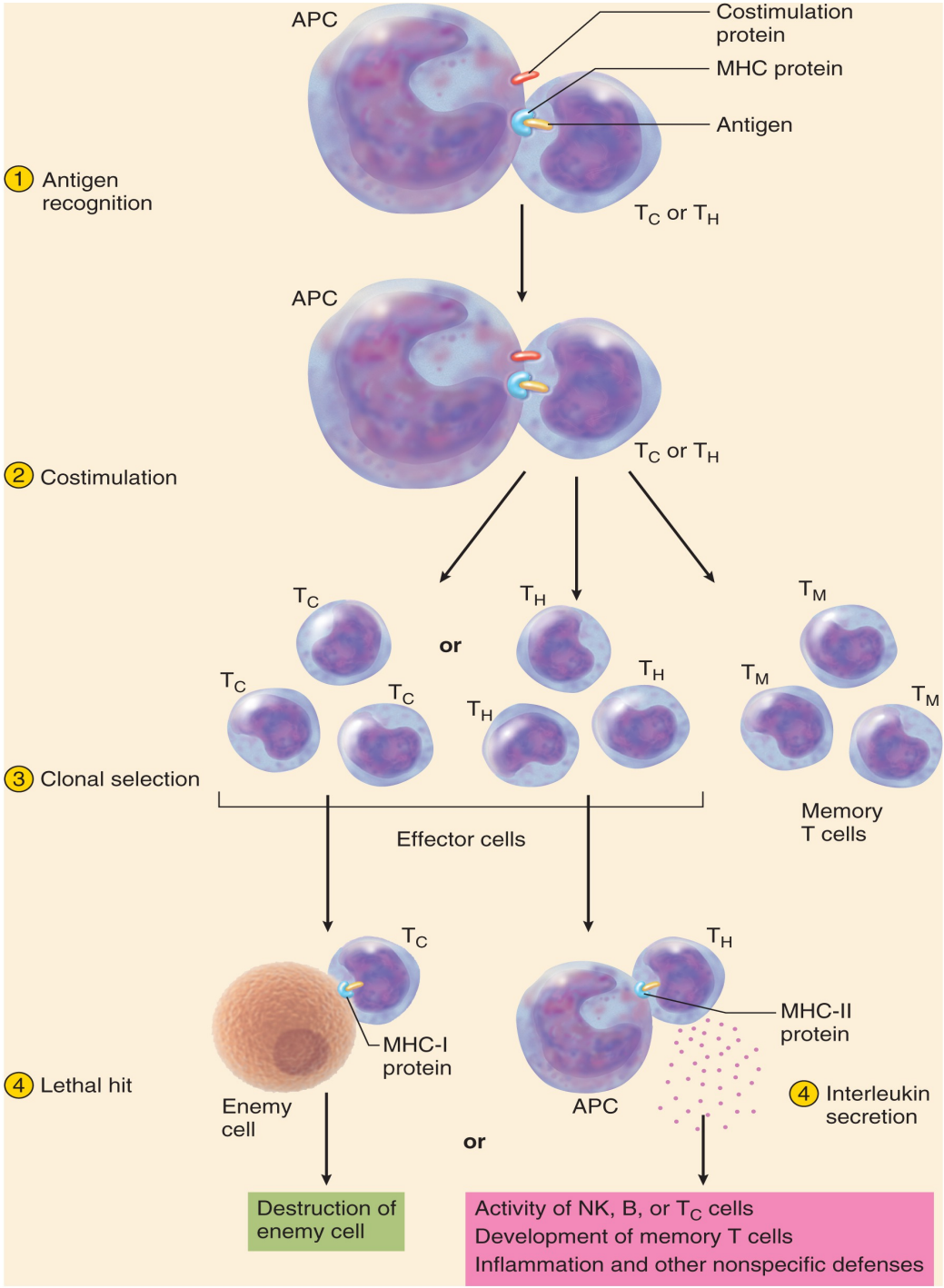
Activation of Cytotoxic T Cells

- The first step to activate CD8-Tc occurs when they bind to a dendritic cell that displays foreign epitope in Class-I MHC (note: dendritic cells have both class I and II)

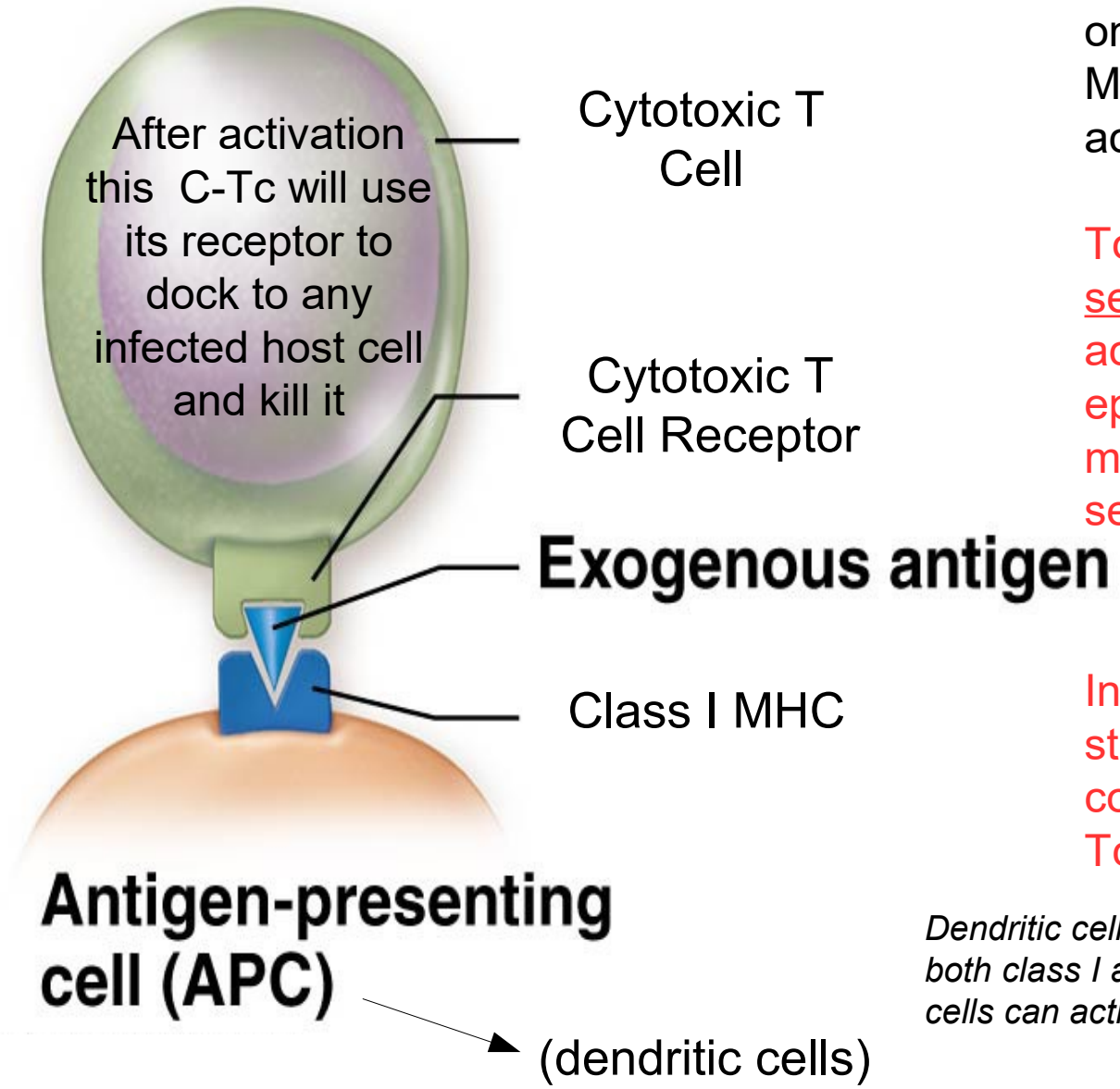
- Note CD8 protein on T cell binds to dendritic cell costimulation protein = “second check” for proper MHC-I receptor complex = costimulation

- Now cytotoxic T cell (Tc) starts clonal selection and at same time makes memory Tc

- Clonal selection make “attack” cytotoxic T cells /// These cytotoxic celsl = killer cells /// These activated cytotoxic T cells are now able to dock and but to kill infected cells need a secretion of interleukin-2 from Helper-T cells (also activated by similar epitope)



This is how a naive cytotoxic T cell is activated and initiates clonal selection.

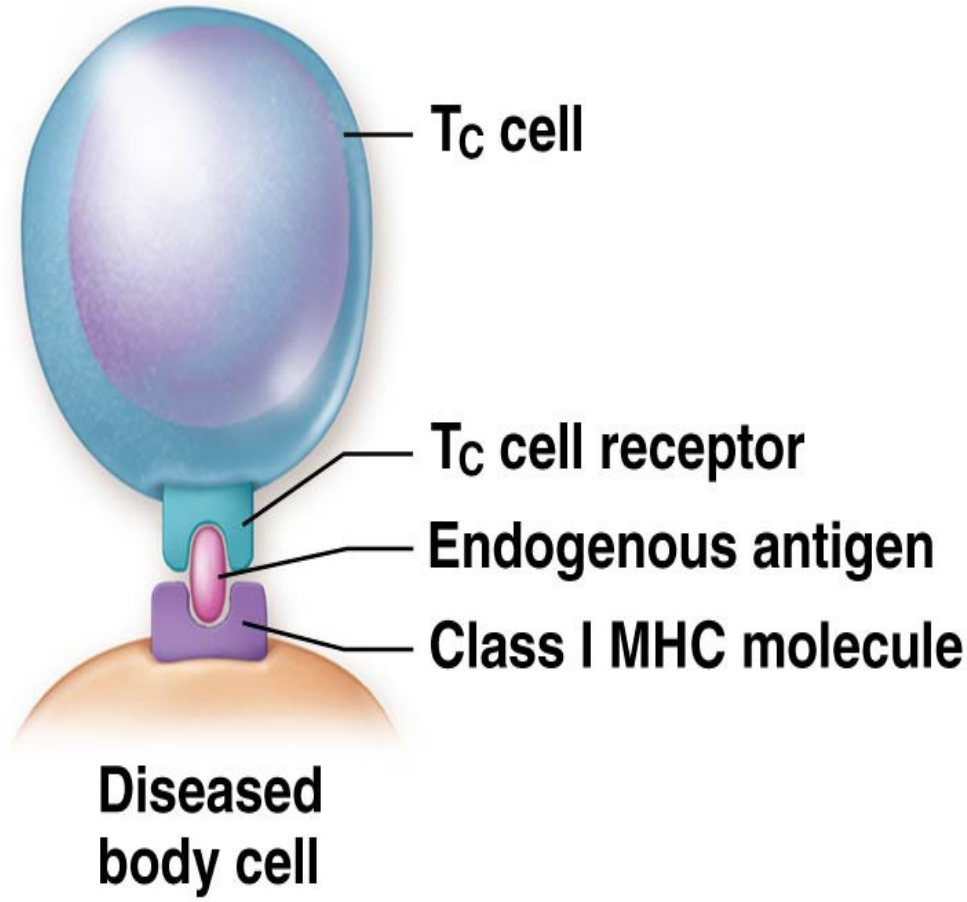


Naive C-Tcells receptors only recognize class I-MHCP // must be activated by dendritic cell

To complete clonal selection of C-Tc // activated H-Tc (by same epitope in a separate mechanism) must secrete interleukin 2

Interleukin 2 is required to start clonal selection // complete activation of C-Tc

Dendritic cells are unique because they have both class I and class II MHCP // dendritic cells can activate both C-Tc and H-Tc



After a Cytotoxic-T cell is activated and undergoes clonal selection the host will now have millions of “killer” cytotoxic-T-cells

These fully activated C-Tc may now directly dock onto diseased body cells showing epitope in class-I-MHC and kill these infected cells

After docking the C-Tc gives the “kiss of death”

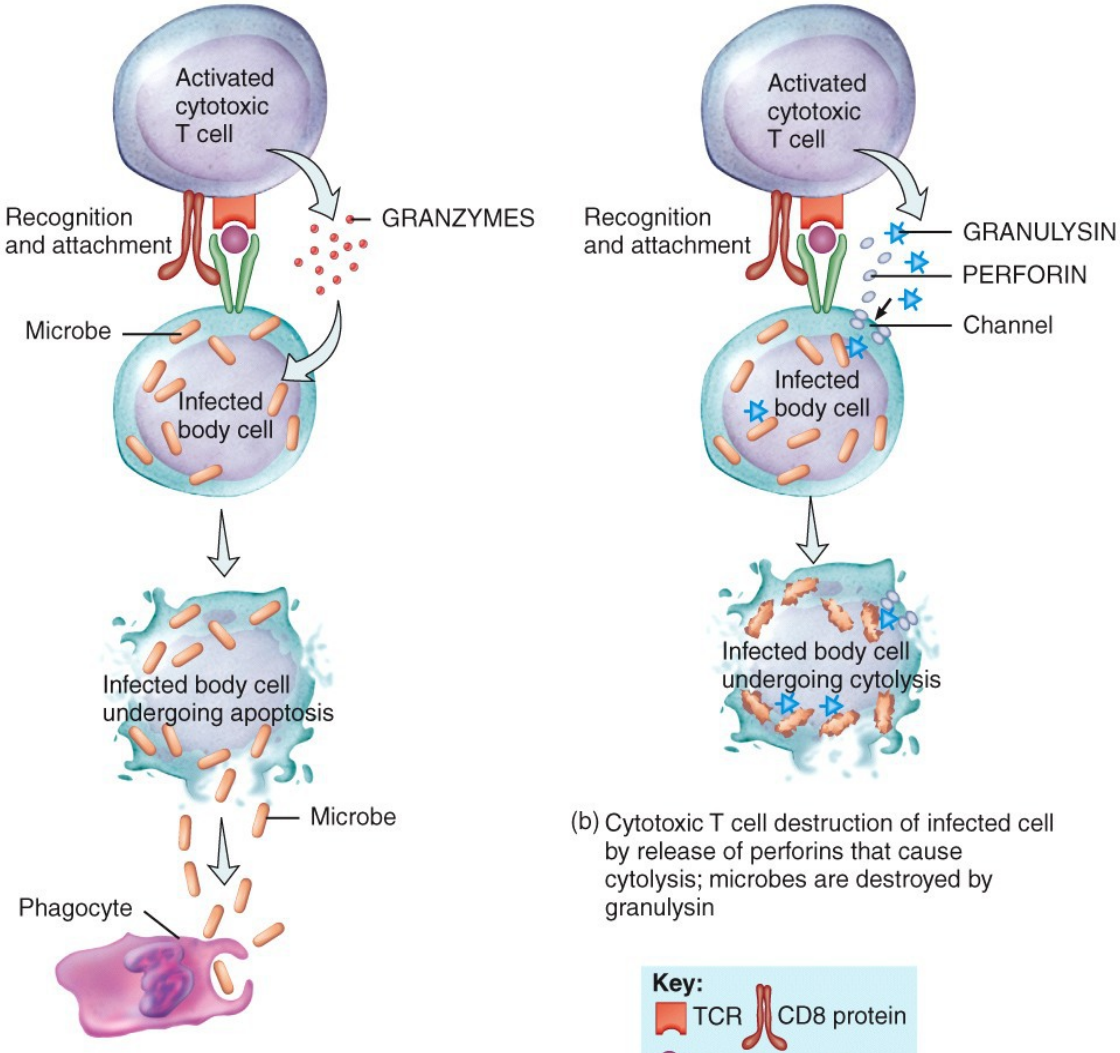
Endogenous means these proteins are from the host cells' cytoplasm

The Kiss of Death Delivered by the Cytotoxic T Cells

This is the react stage of the “three R”

Two different methods maybe used to destroy infected cells with endogenous foreign antigen

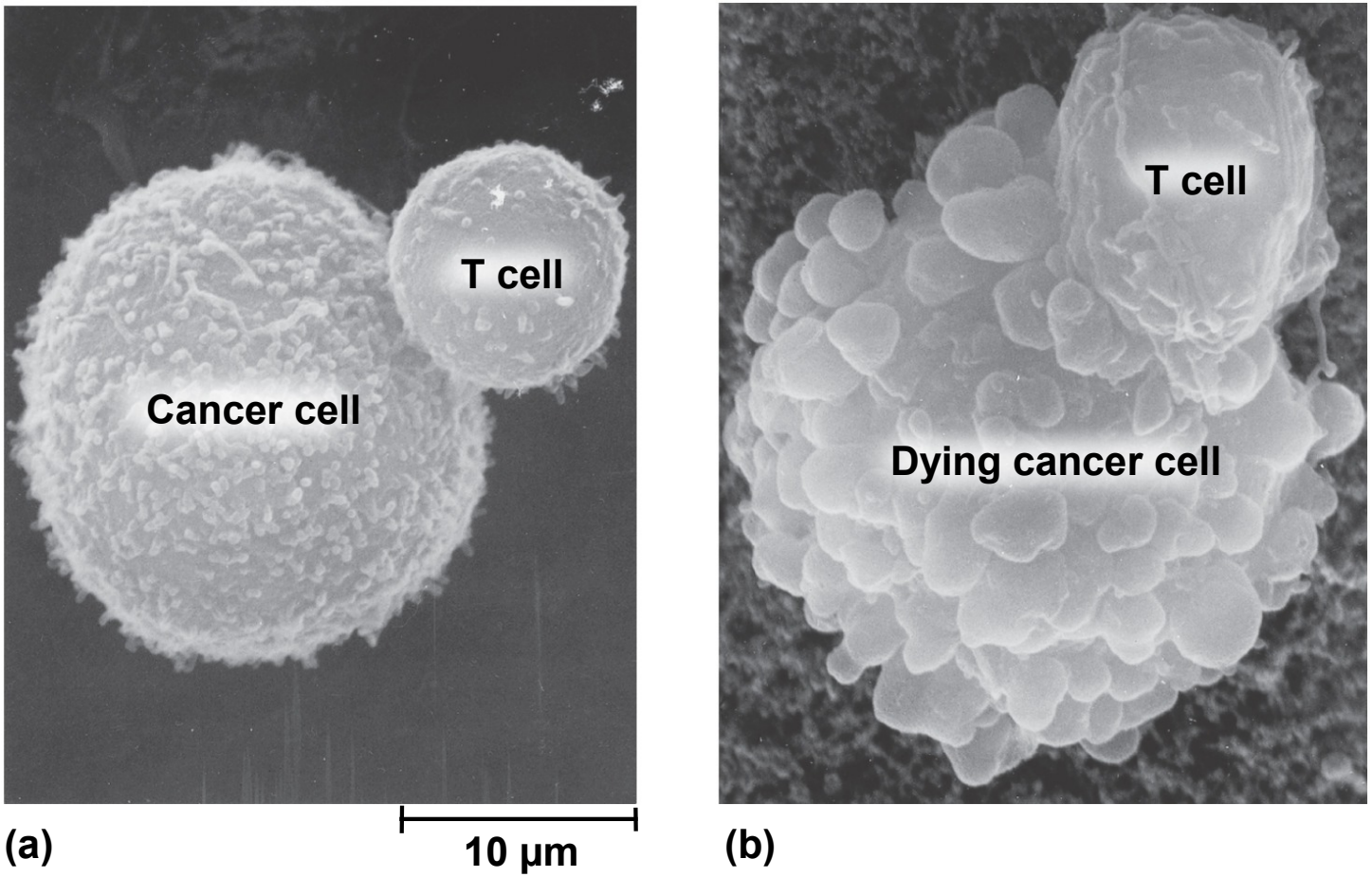
There is also a third way for C-Tc to kill host cells by releasing cytokines (e.g. cytokine storm)



(a) Cytotoxic T cell destruction of infected cell by release of granzymes that cause apoptosis; released microbes are destroyed by phagocyte

(b) Cytotoxic T cell destruction of infected cell by release of perforins that cause cytolysis; microbes are destroyed by granulysin

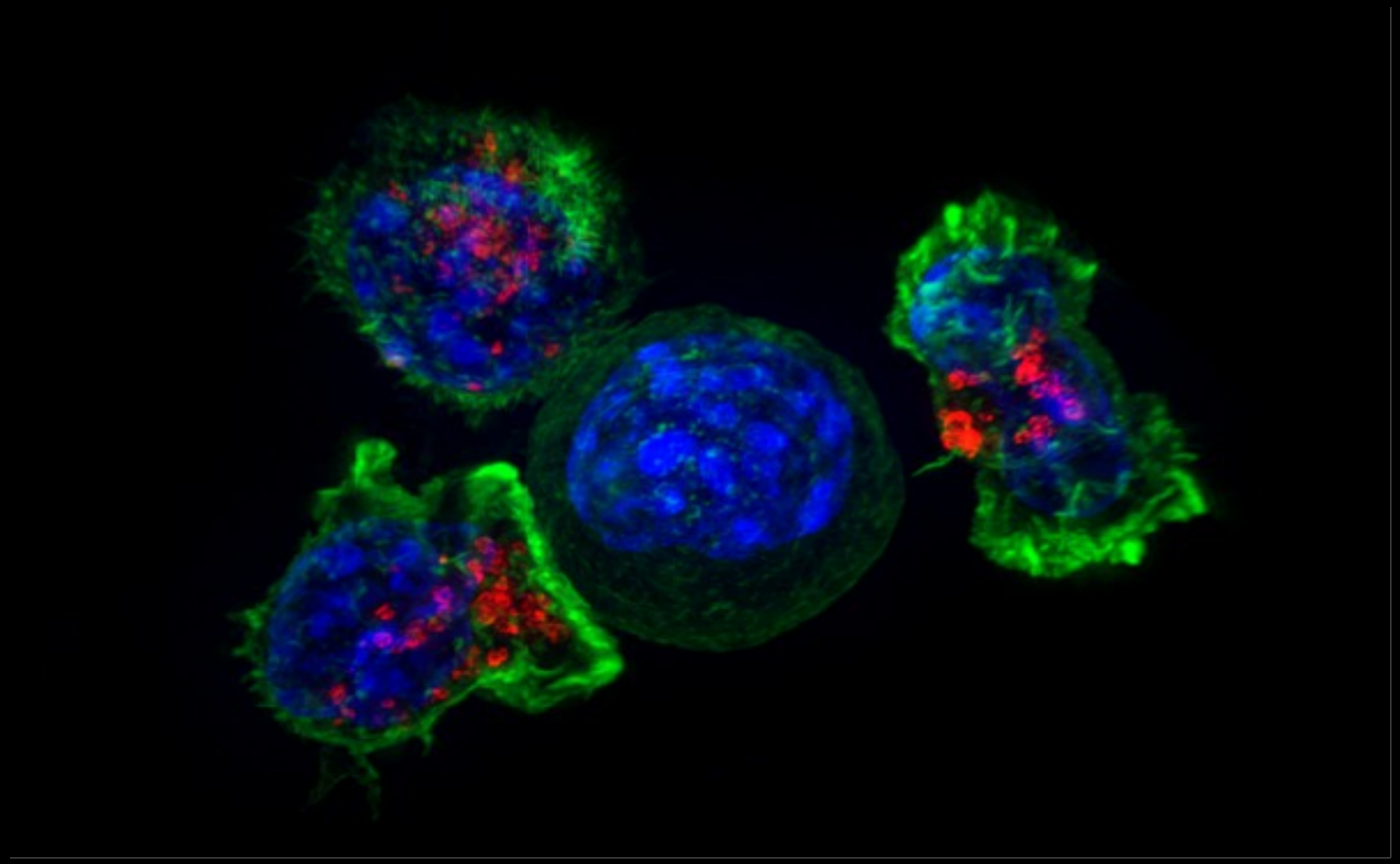
Cytotoxic T Cell Function



Dr. Andrejs Liepins

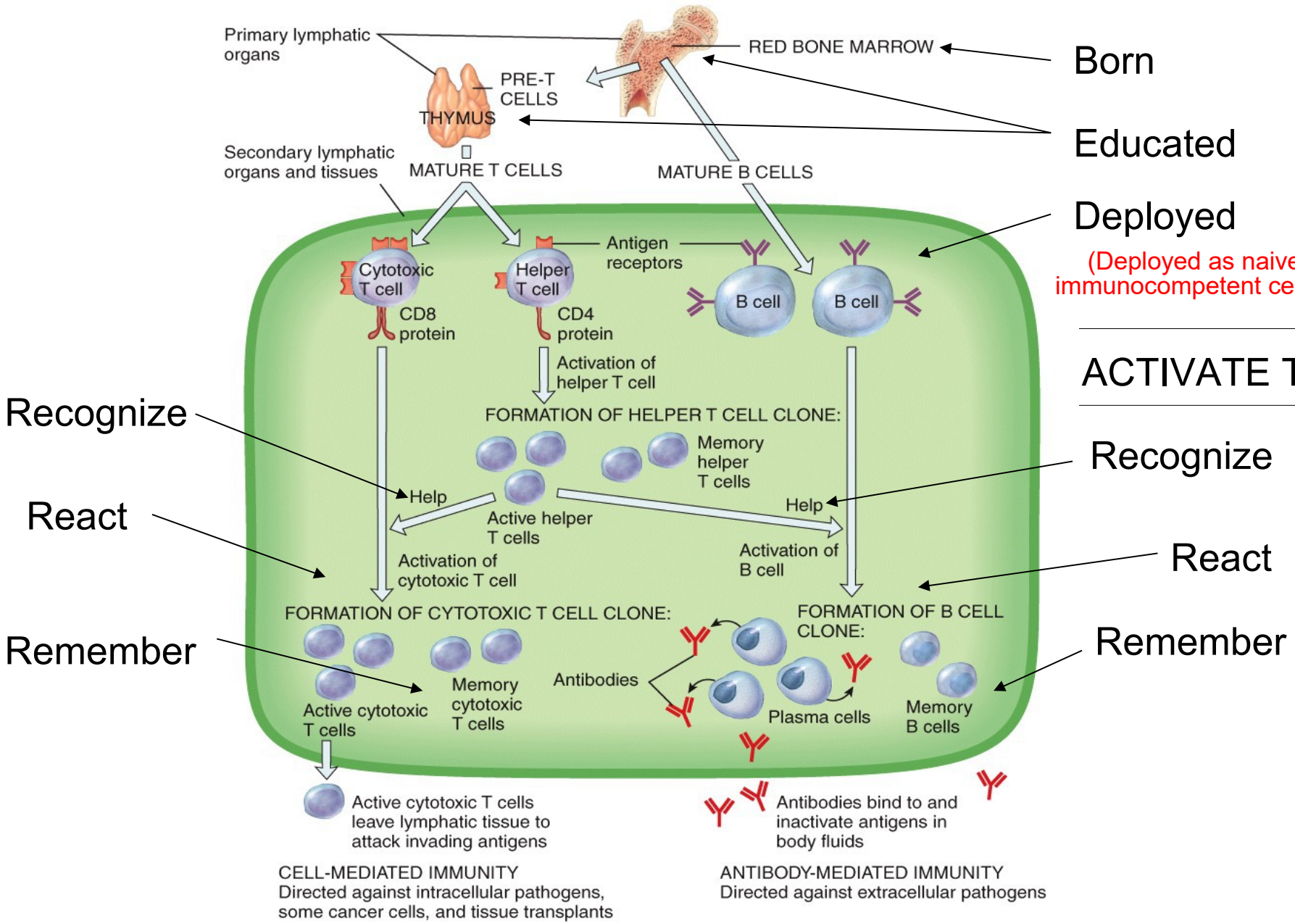
- cytotoxic T cell binding to cancer cell

Cytotoxic T Cells Attacking Cancer Cell



In this immunofluorescence image, a group of killer T cells (outer three) are engaging a cancer cell (centered one). A patch of signaling molecules (pink) that gathers at the site of cell-cell contact indicates that the CTL has identified a target. Lytic granules (red) that contain cytotoxic components then travel along the microtubule cytoskeleton (green) to the contact site and are secreted, thus killing the target.

Outline for the structure and function of acquired immunity.



How are B cells activated?

Humoral immunity requires the action of B cells

Different classes of B cells (plasma cells, memory B cells, regulatory B cells)

Each class has a special function

*Plasma cells are formed from B cells /// **it is the plasma cells that make antibodies** // each plasma cell make 2,000 antibodies per second for approximately 7 days*

Antibodies attach to foreign antigen /// render foreign antigen harmless and tag pathogen for destruction

Note: antibodies don't kill anything /// antibodies activate complement and complement kills the pathogen

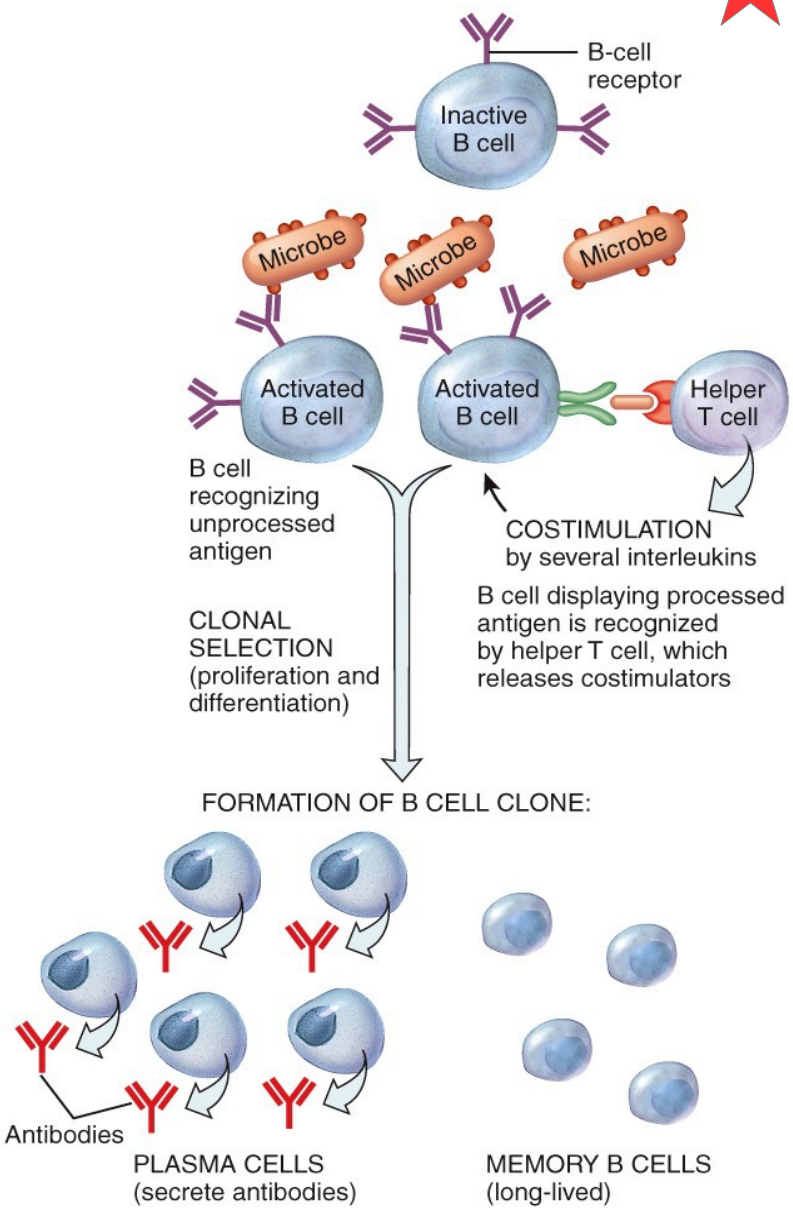
Activation of B Cells

The B cell "recognition" process for activation is different than the Tc process.

Naïve immunocompetent B cells have two distinct activation pathways with different outcomes // H-T cell dependent and H-T cell independent.

If B cells enter clonal selection without the Helper T cell – (no costimulation known as H-T cell independent) then… /// the B cell activation is less robust /// results in fewer plasma cells and less antibodies /// but no B memory cells are formed

If B cells enter clonal selecton with the assistance of Helper T cells – with costimulation - then.... /// stronger response with many more plasma cells formed, more antibodies formed and memory B cells formed.



Activation of B Cells

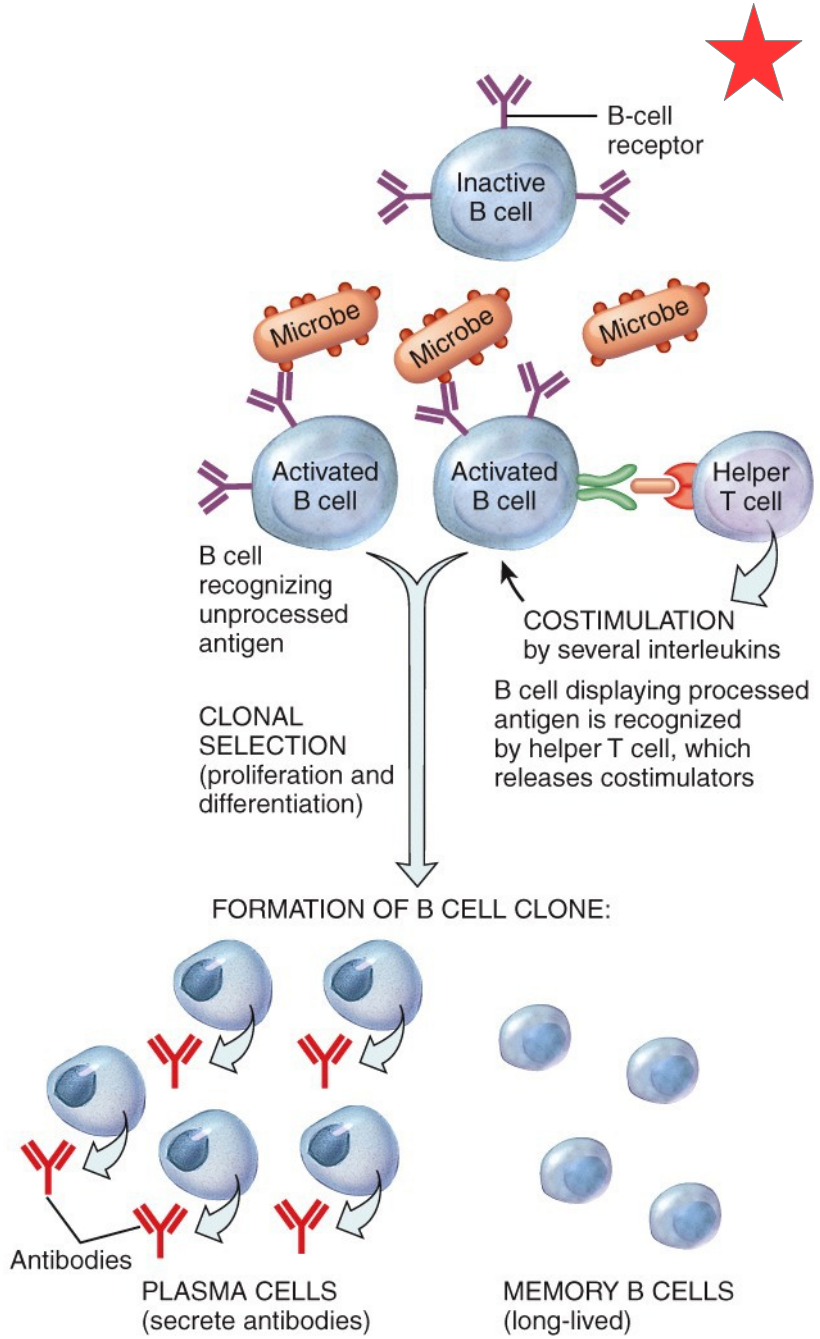
First step in “recognition” (activation) is pathogen binds to a B cell receptor.

B cell now will act as an APC and engulphs pathogen /// processes antigen and presents epitope on its plasma membrane

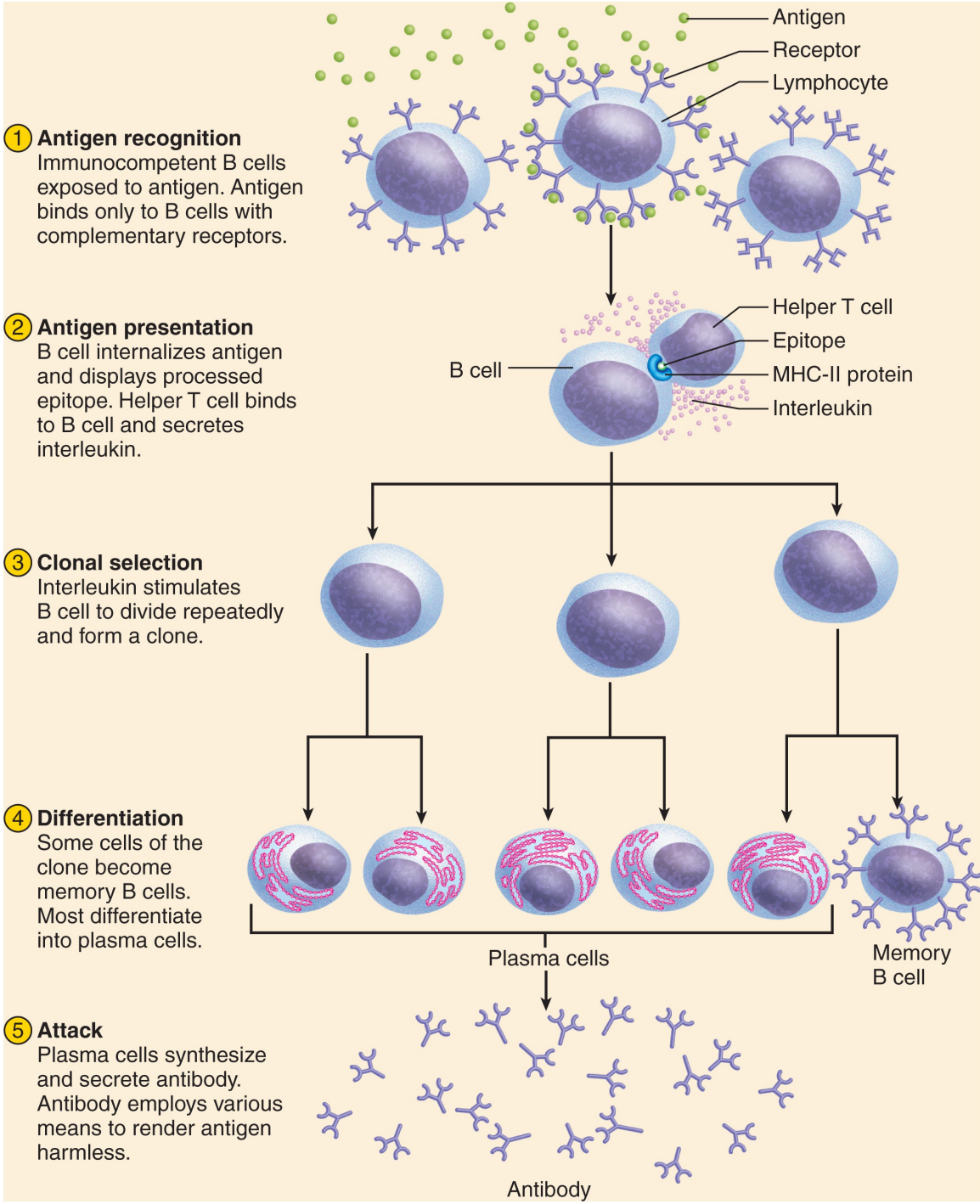
Previously activated Helper T cell with similar pathogen now binds it's T cell receptor with MHCP-II-epitope complex (second step)

If Helper T cell and B cell complex receives interleukin 2 and other secretions from T_H ithen B celll undergoes costimulation

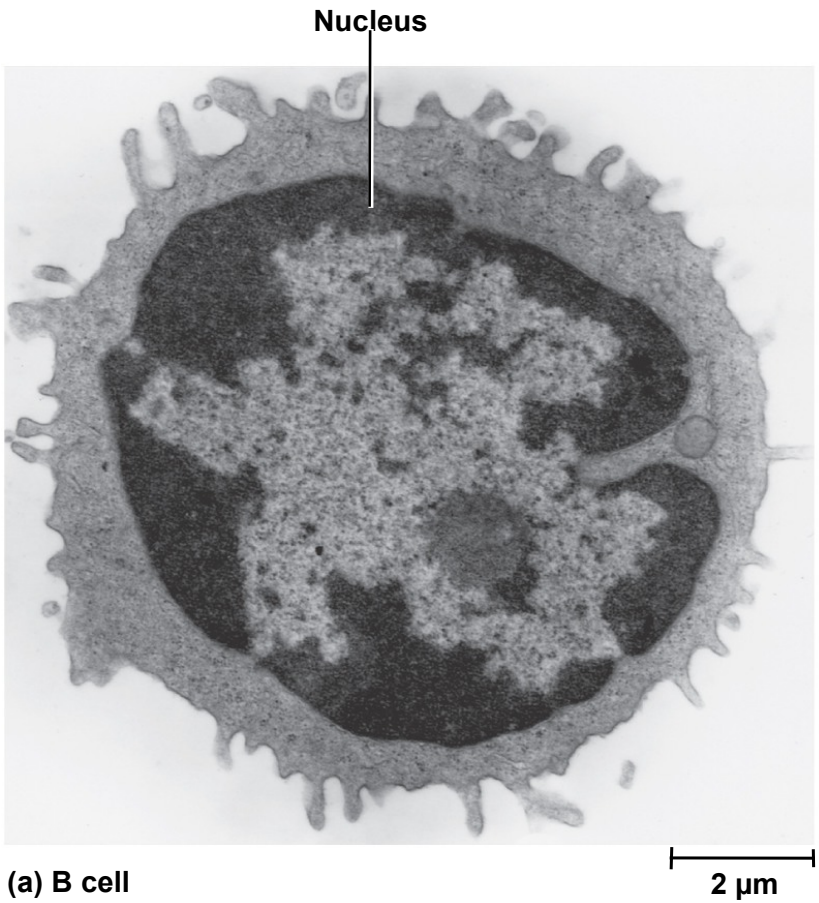
Plasma cells and memory B cells formed // Plasma cells make <u>2,000 antibodies per second per cell for 7 days.</u>



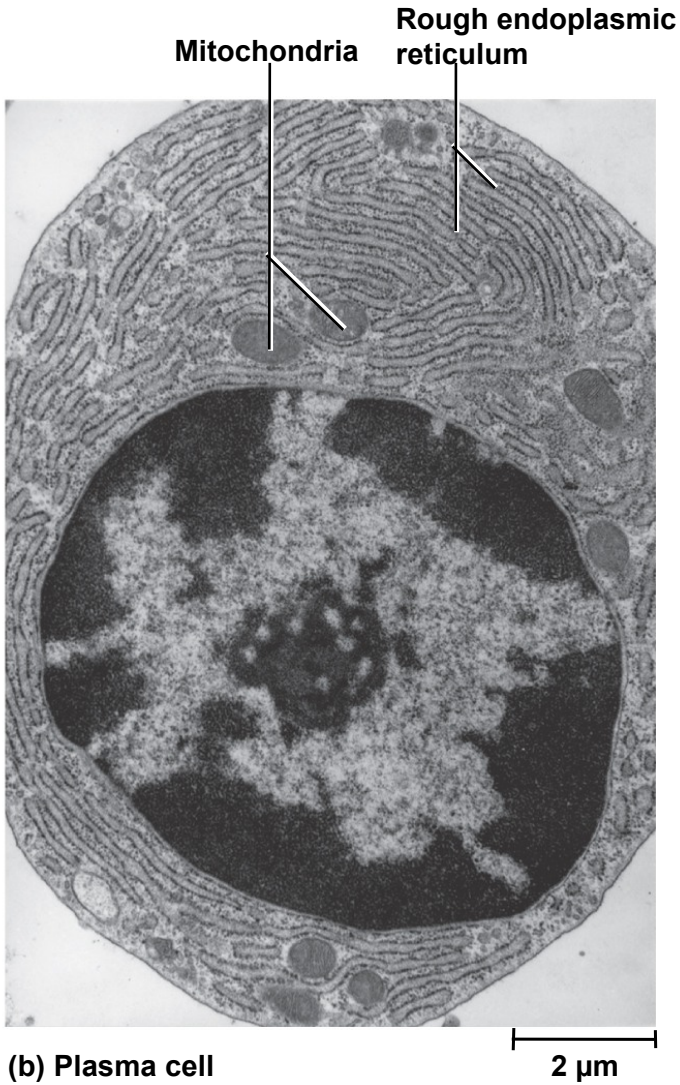
B Cells to Plasma Cells



B cells to Plasma cells



(a) B cell



(b) Plasma cell

Can you explain the structure and function relationship?

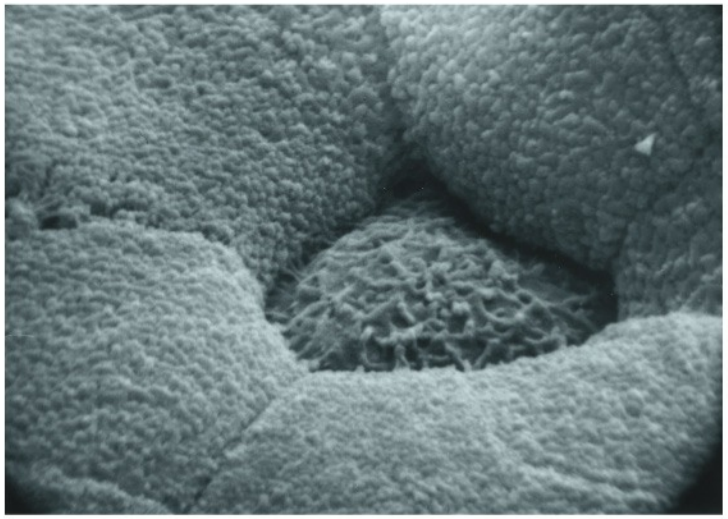
M Cells

This is how immune cells try to find out (i.e. recognize) what type of pathogens may “break into” the sterile compartments of your body.

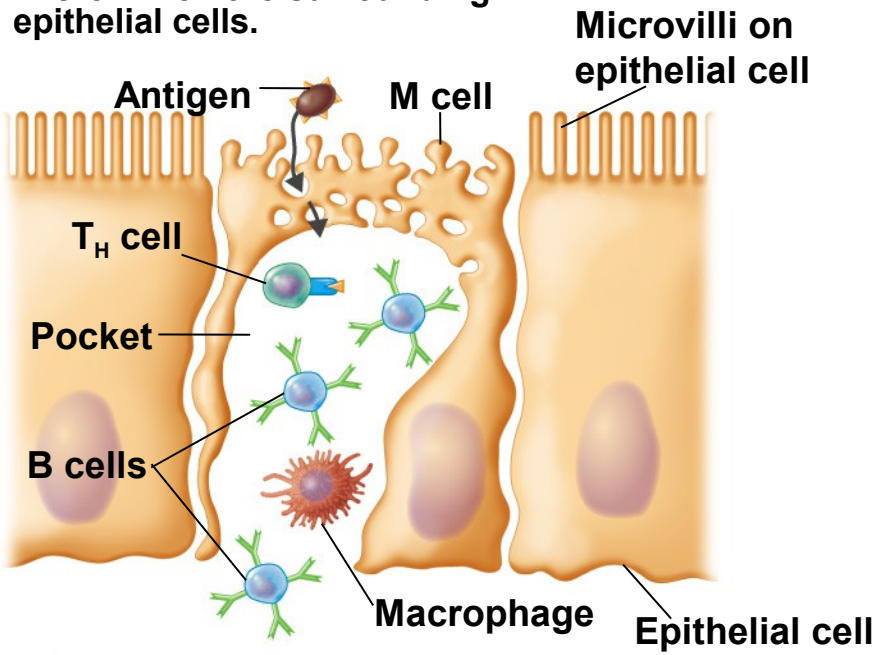
Immune system recognize bacteria even before it is in our bodies

Immune system starts to prepare defenses against bacteria.

Tonsils have a similar function in bucal cavity!



(a) M cell on Peyer’s patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells.



(b) M cells facilitate contact between the antigens passing through the intestinal tract and cells of the body’s immune system.

How Can We Use This Knowledge to Cure Cancer

- For decades we have tried to cure cancer with surgery, radiation, and chemotherapy. These options have often caused significant damage to the patient and failed to provide a lasting cure.

- Today we are on the threshold of understanding how to use our C-Tc and B-cells to kill cancer cells.

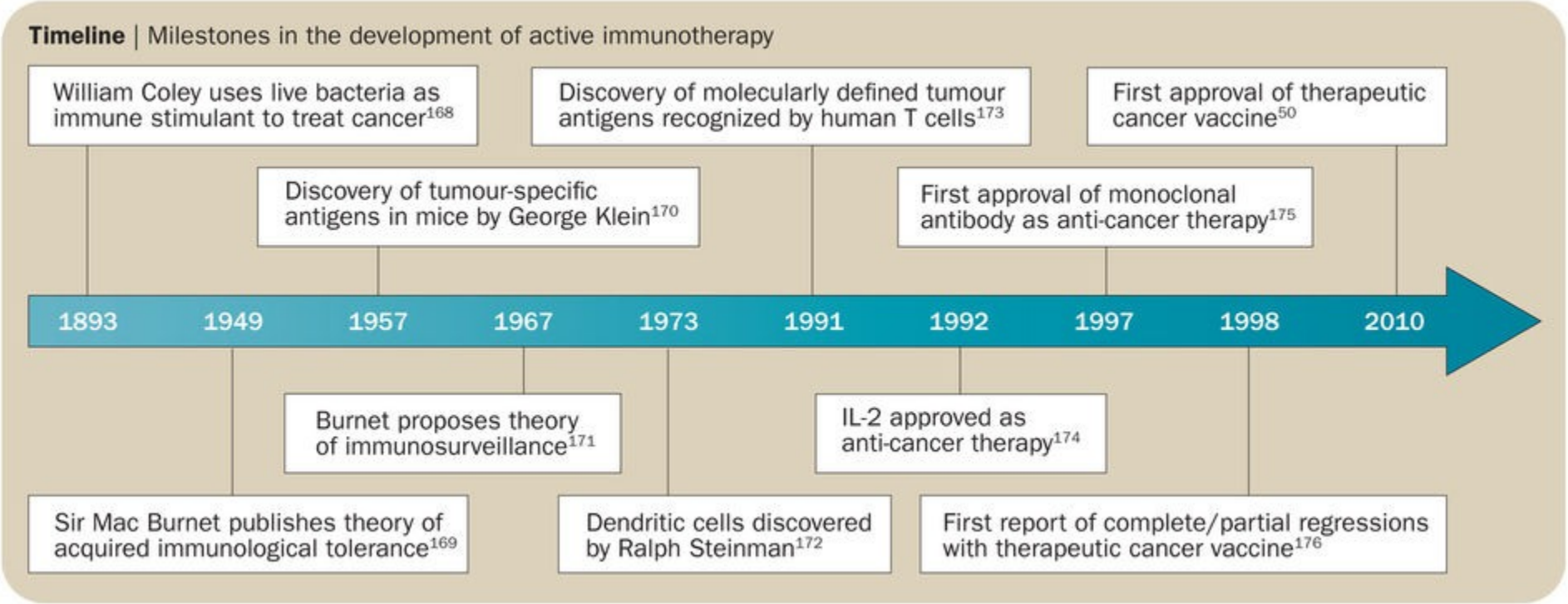
- Cancer immunotherapy is able to leverage our knowledge about the immune system to direct the immune system cells to identify “specific types of molecules only found on cancer cells” and inhibit cancer cells ability to turn off our immune cells from attacking cancerous cells.

- These new cancer immunotherapy's target only cancerous cells.

- Early “clinical trials” have demonstrated that we can kill some types of cancer cells using our immune cells. These new therapies now offer people diagnosed with certain types of cancers a viable cure.

- New Therapies = Checkpoint Inhibition, Dendritic Cell Vaccines, and CAR T Cells

See Next Slide


Timeline | Milestones in the development of active immunotherapy
William Coley uses live bacteria as immune stimulant to treat cancer[168]
Discovery of molecularly defined tumour antigens recognized by human T cells[173]
First approval of therapeutic cancer vaccine[50]
Discovery of tumour-specific antigens in mice by George Klein[170]
First approval of monoclonal antibody as anti-cancer therapy[175]
1893
1949
1957
1967
1973
1991
1992
1997
1998
2010
Burnet proposes theory of immunosurveillance[171]
IL-2 approved as anti-cancer therapy[174]
Sir Mac Burnet publishes theory of acquired immunological tolerance[169]
Dendritic cells discovered by Ralph Steinman[172]
First report of complete/partial regressions with therapeutic cancer vaccine[176]

THREE IMMUNE STRATEGIES

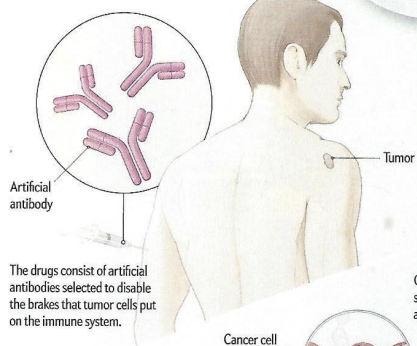
Surgery, radiation and chemotherapy have long served as the standard treatments against cancer. But clinical trials over the past five years have shown that supercharging the body's immune cells—which evolved to fight harmful bacteria and viruses, among other things—offers a powerful new addition to the mix by helping the cells to find and destroy tumors. The approaches shown here are being tested alone or in combination with other treatments.

How is immunotherapy changing the treatment of solid tumors?

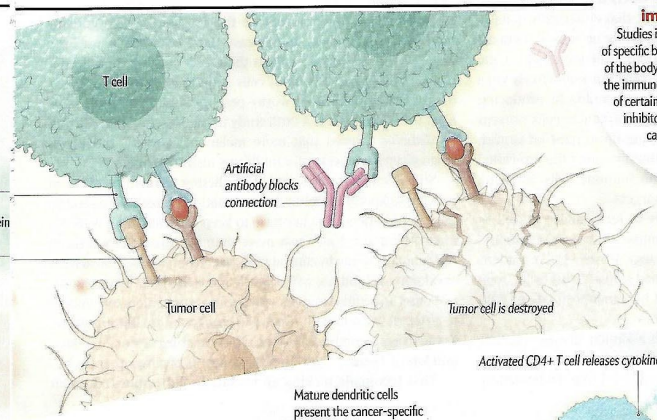
Cancers of the skin, lungs and other tissues are called solid tumors because they form a mass that creates its own protective environment. Checkpoint inhibitors help to disrupt this environment, eliminating advanced skin tumors for one in five patients in clinical trials.

Checkpoint Inhibitors

Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor. New drugs—called checkpoint inhibitors—disable the cancer cells' immune-dampening signals, allowing the immune system to do its job.



The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.



Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.

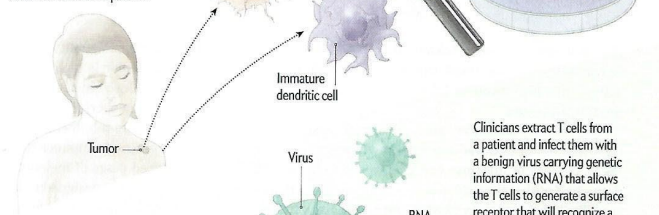
By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.

Could intestinal bacteria boost the effectiveness of immune treatments?

Studies in mice suggest that the presence of specific bacterial species in the intestine (part of the body's so-called microbiome) may boost the immune system's ability to slow the growth of certain types of tumors. Also, checkpoint inhibitors do a better job of eliminating cancer in rodents that harbor these bacteria.

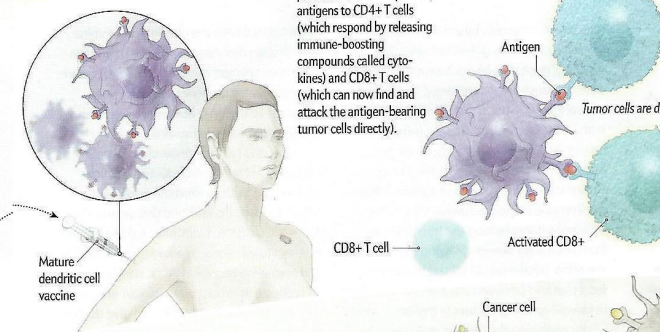
Dendritic Cell Vaccine

Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dendritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.

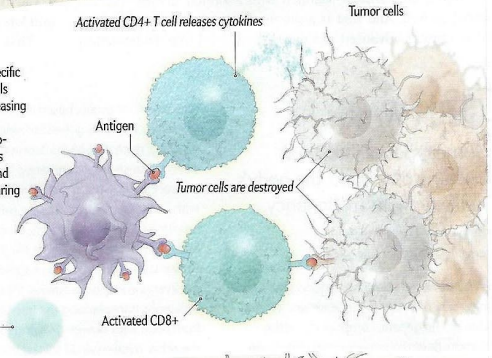


Researchers extract healthy cells, cancer cells and immature dendritic cells from a patient.

Researchers compare the genetic blueprints of malignant and healthy cells, looking for information about antigens that are found only on the cancer cells. These antigens are added to the dendritic cells, which absorb them. The now mature dendritic cells are then reinjected.

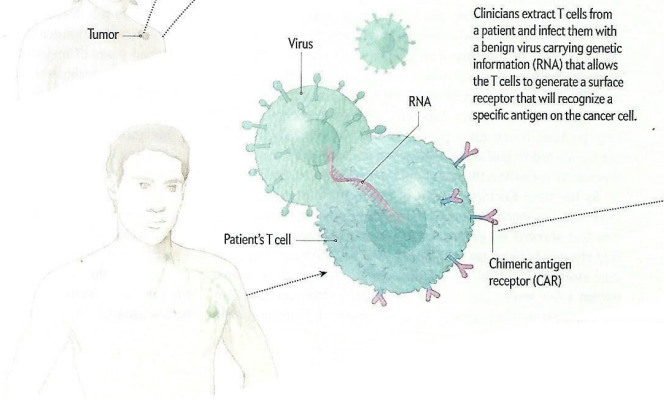


Mature dendritic cells present the cancer-specific antigens to CD4+ T cells (which respond by releasing immune-boosting compounds called cytokines) and CD8+ T cells (which can now find and attack the antigen-bearing tumor cells directly).

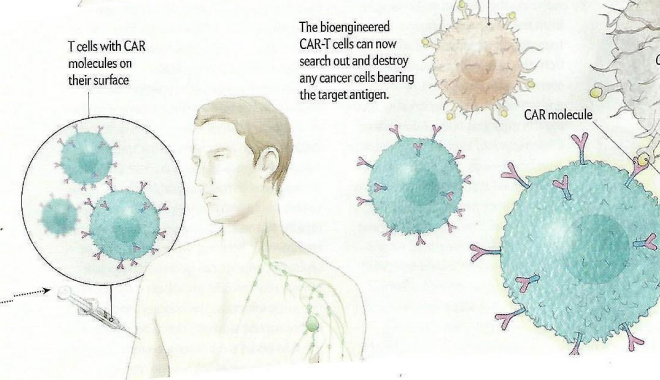


CAR-T Cells

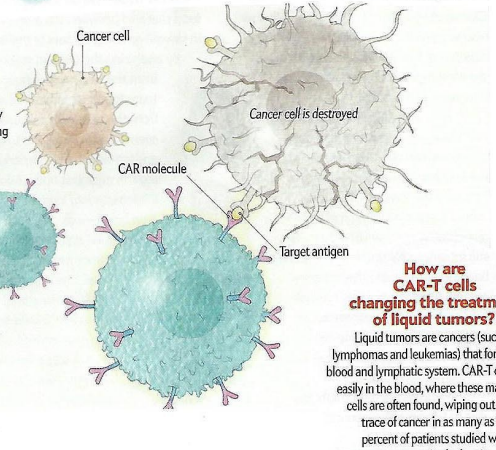
Chimeric antigen receptor (CAR) T cells combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy any cells that bear the target antigen. This mishmash eliminates intermediate steps typically taken by B and T cells, making CAR-T cells virtually unstoppable.



Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (RNA) that allows the T cells to generate a surface receptor that will recognize a specific antigen on the cancer cell.



The bioengineered CAR-T cells can now search out and destroy any cancer cells bearing the target antigen.



How are CAR-T cells changing the treatment of liquid tumors?

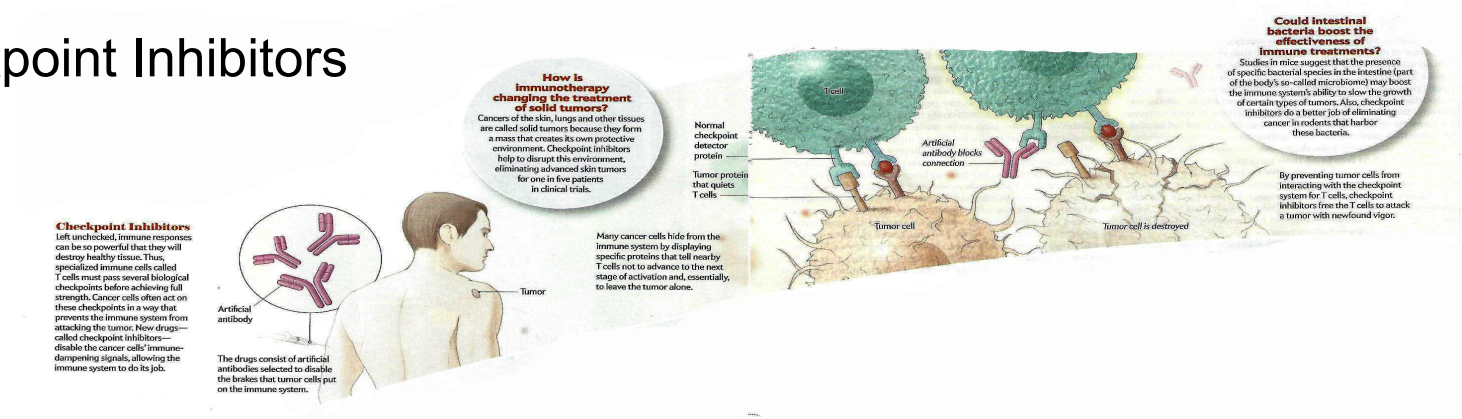
Liquid tumors are cancers (such as lymphomas and leukemias) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer in as many as 90 percent of patients studied with an aggressive leukemia.

2016 FUTURE OF MEDICINE

Illustration by Shizuka N. Aoki

See Next Set of Slides

Checkpoint Inhibitors



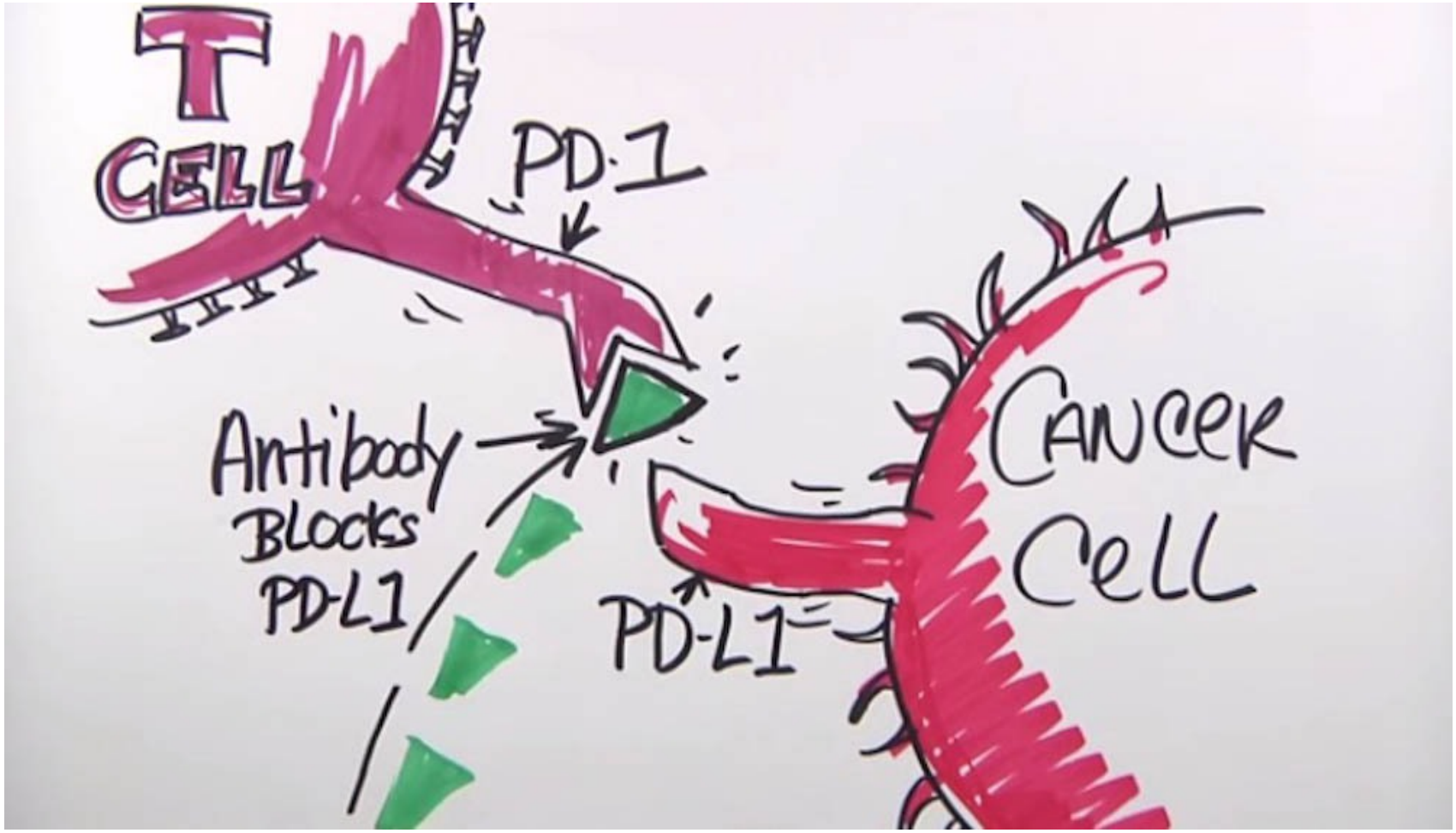
Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T-cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor.

New drugs called checkpoint inhibitors, disable the cancer's immune dampening signals to allow the immune system to do its job. The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.

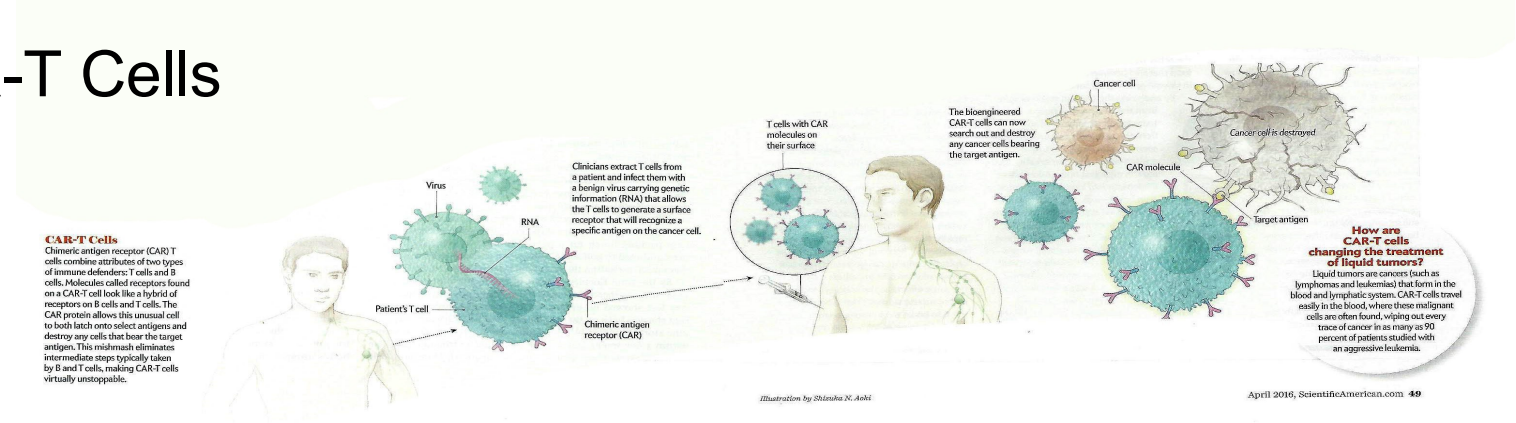
Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next state of activation and essentially, to leave the tumor alone. By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.

Cancer of the skin and other tissue are called solid tumors and create its own protective environment. Checkpoint inhibitors disrupt this environment to eliminate these solid tumors in 20% in clinical trials.

Checkpoint Inhibitors



CAR-T Cells



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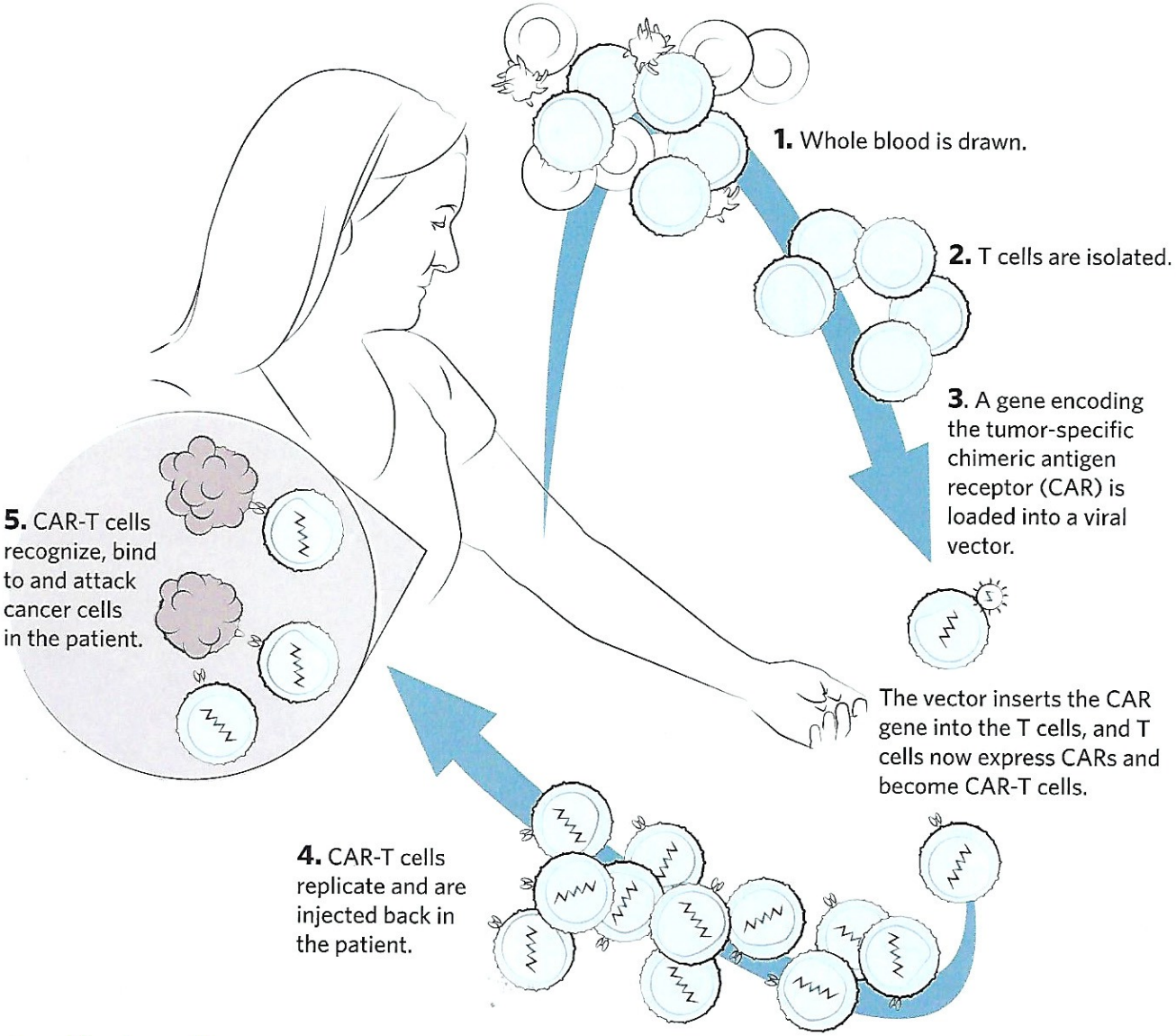
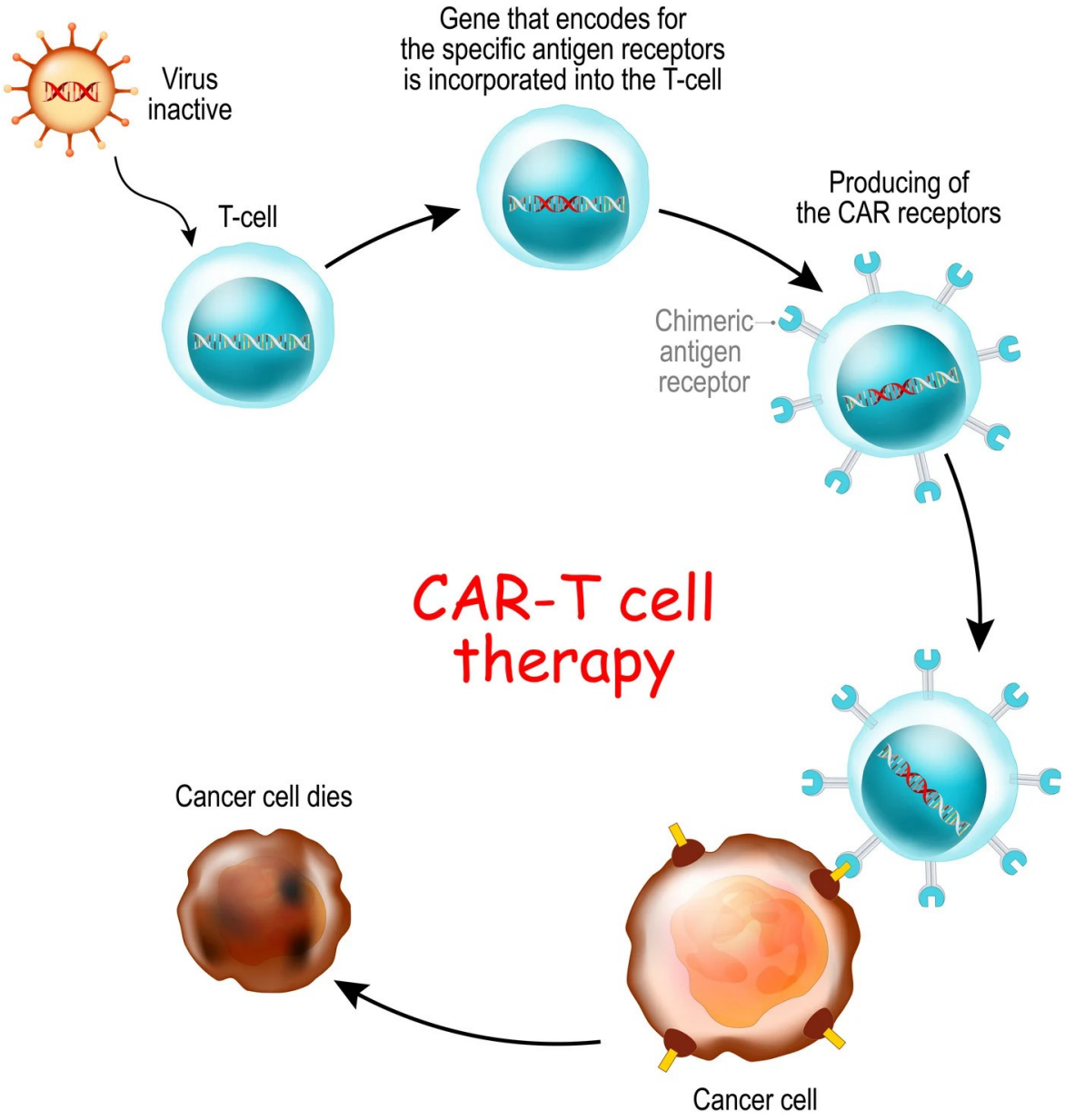
Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (mRNA) that allows the T cell to generate a surface receptor that will recognize a specific antigen on the cancer cell. The bioengineered CAR-T cells can now be injected back into the patient and search out and destroy any cancer cells bearing the target antigen.

Liquid tumors are cancers (lymphomas and leukemias) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer with 90 percent success.

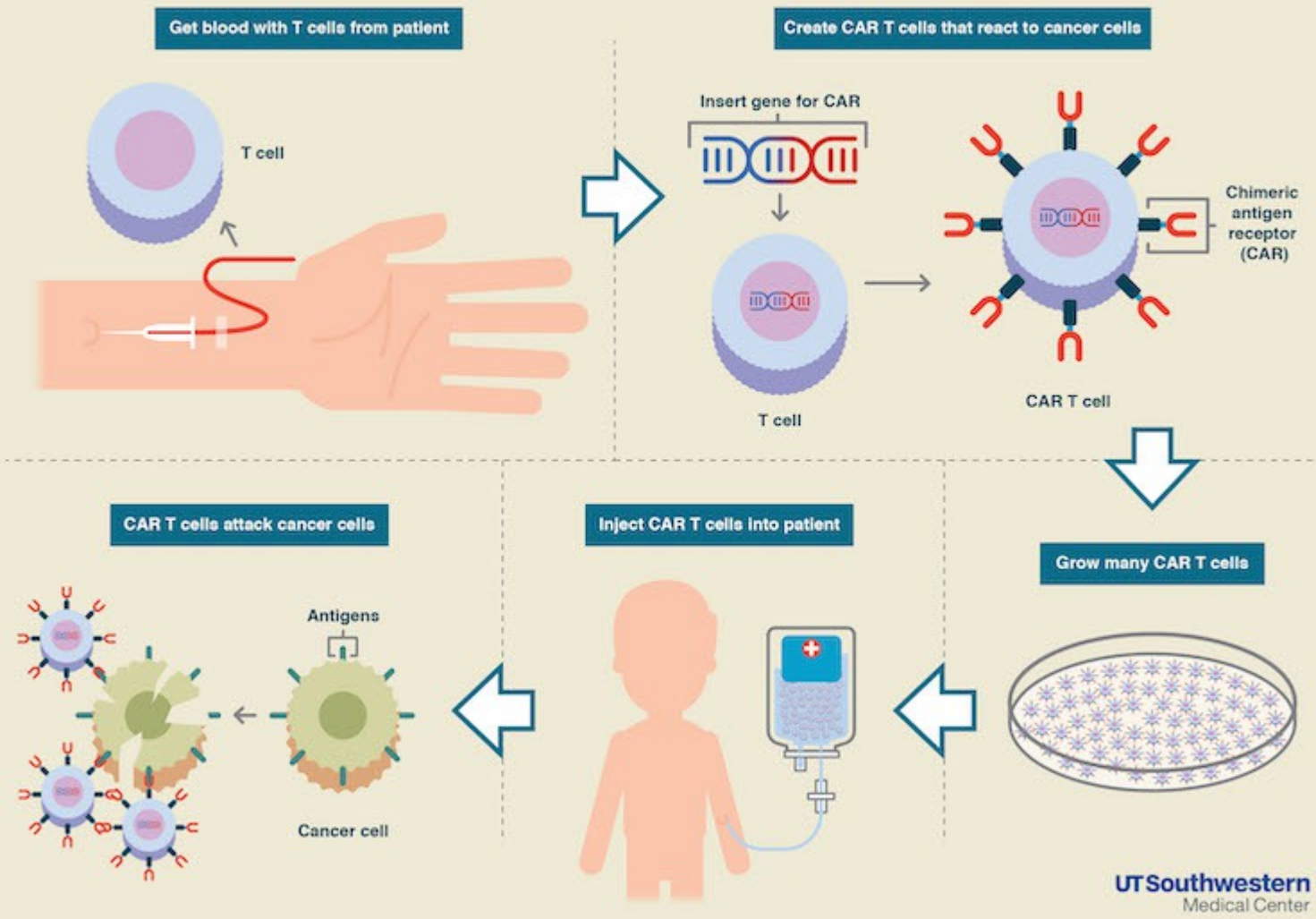
How CAR-T Therapy Works

CAR-T—the initial class of T cell therapies—harnesses the patient's own immune system to fight certain types of cancer

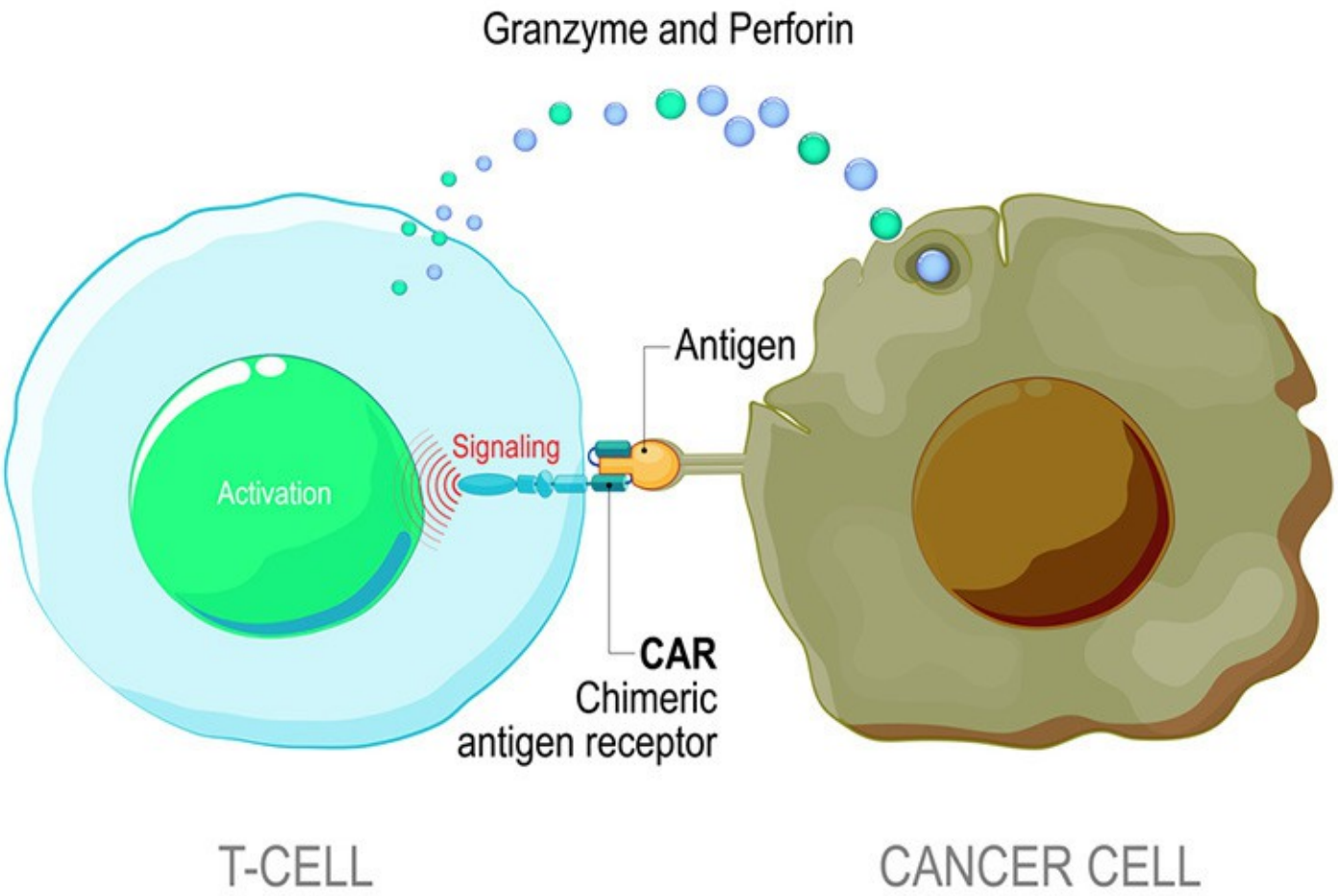



Virus
inactive
T-cell
Gene that encodes for
the specific antigen receptors
is incorporated into the T-cell
Producing of
the CAR receptors
Chimeric
antigen
receptor
CAR-T cell
therapy
Cancer cell dies
Cancer cell

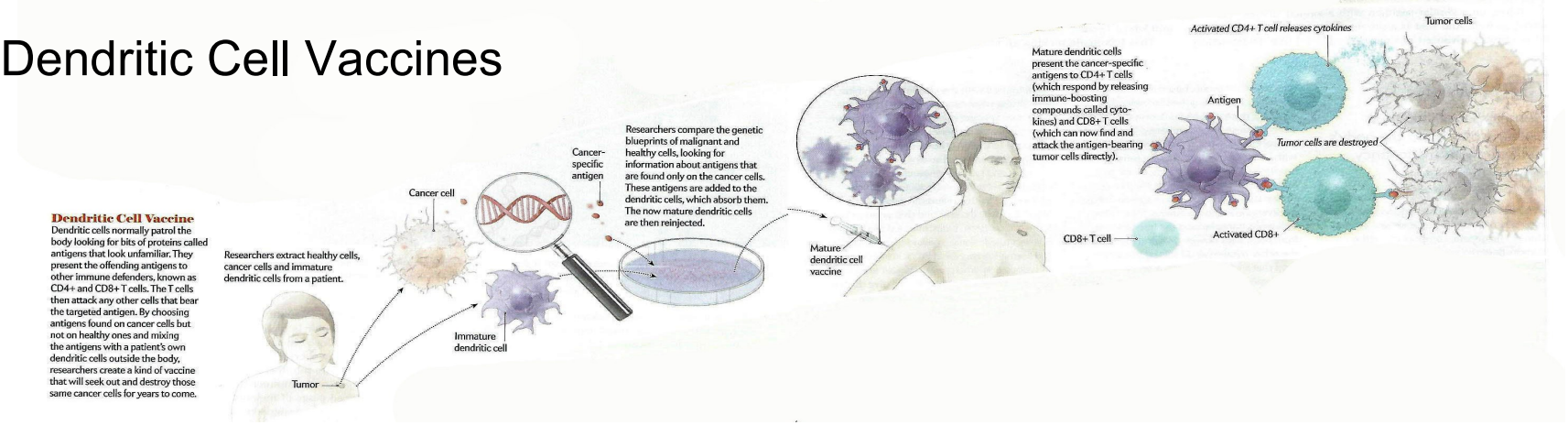
CAR T-cell Therapy



CAR T-cell therapy



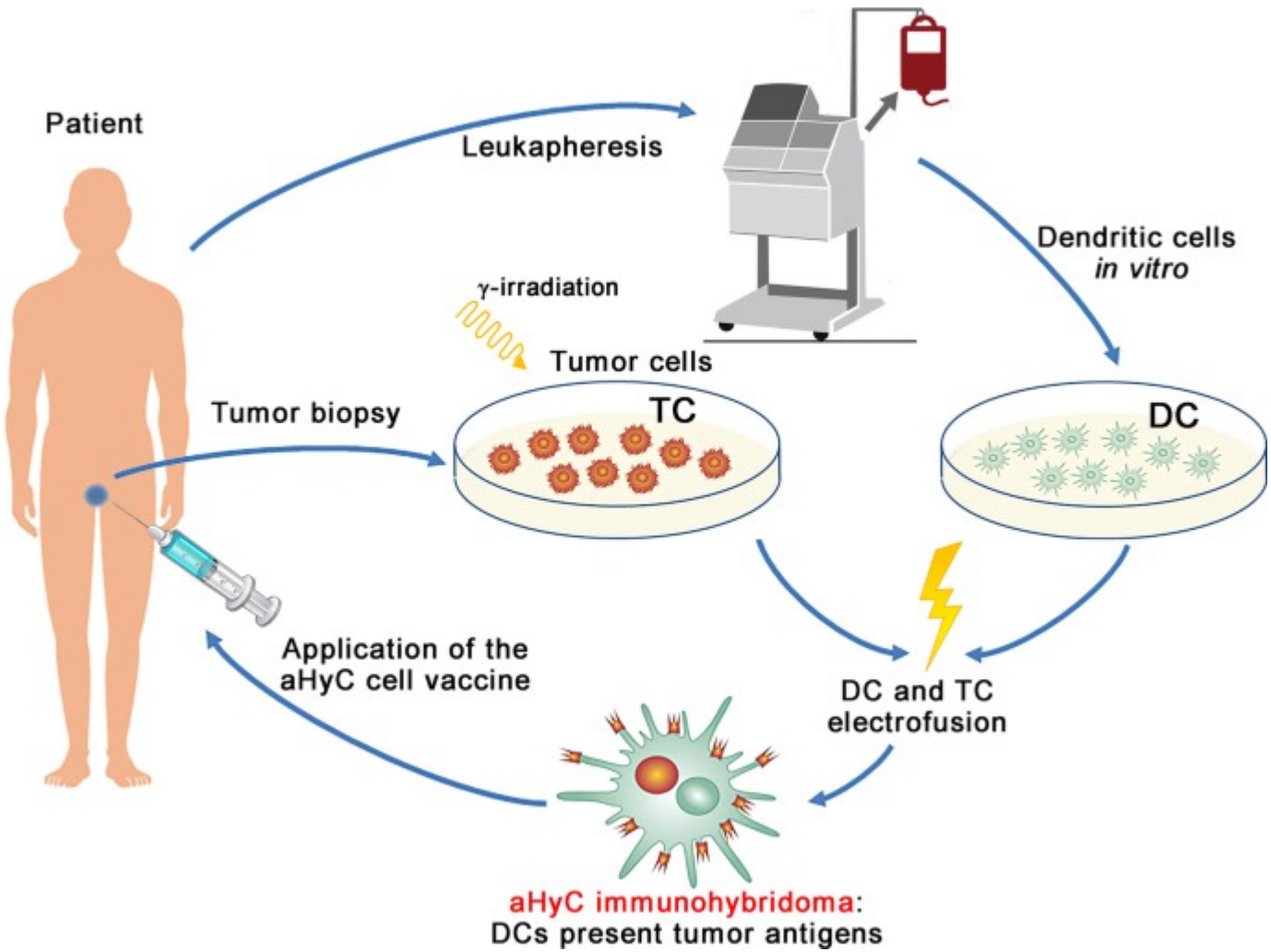
Dendritic Cell Vaccines



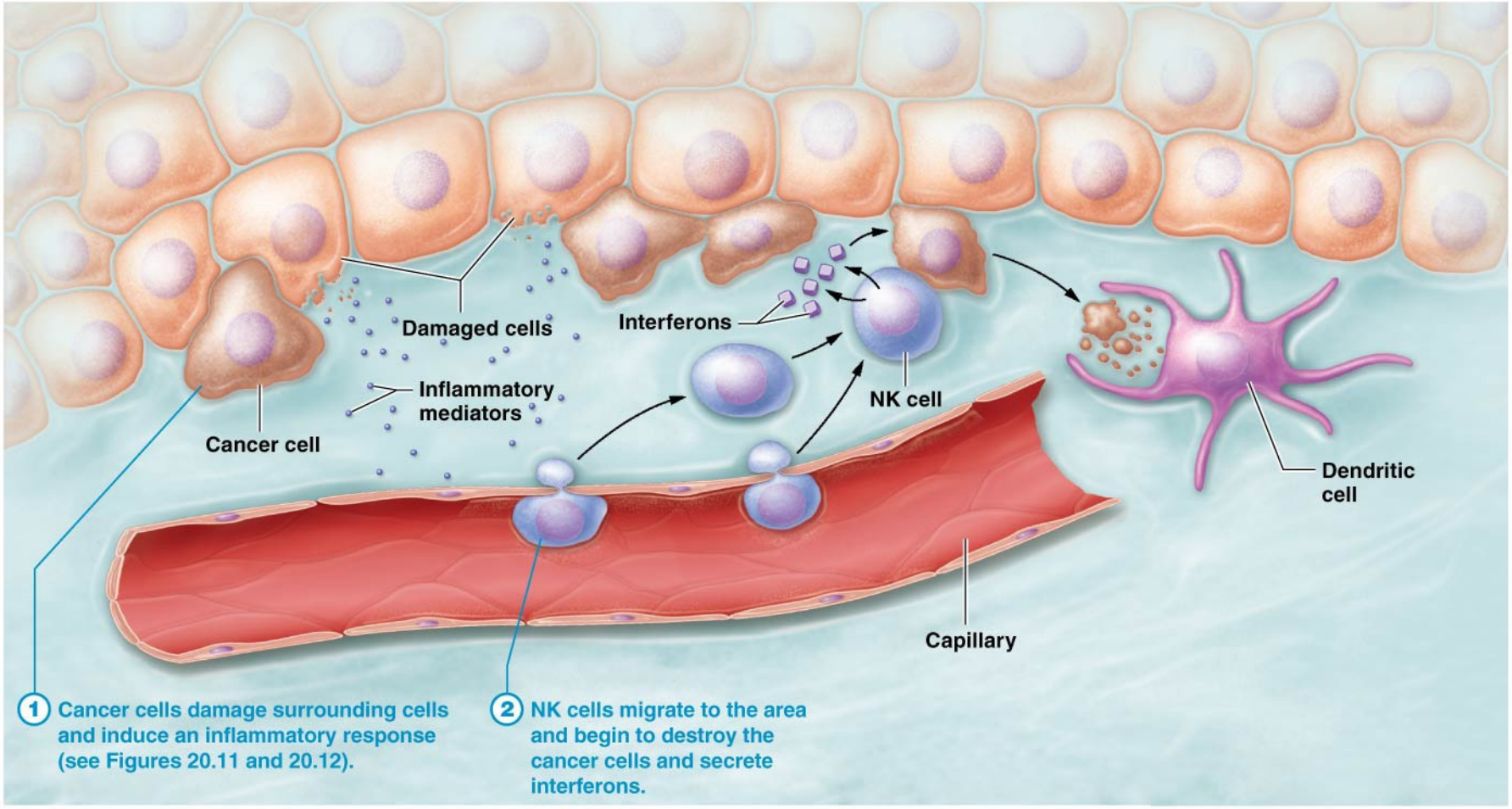
Dendritic cells normally patrol the body looking for bits of protein called antigens that look unfamiliar. They present the offending antigens to other immune defenders, know as CD4 and CD8 T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dedritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.

Researchers extract healthy cells, cancer cells and immune dendritic cells from a patient. Researchers look for antigens only found on cancer cells. These antigens are added to the dendritic cells invitro and the dendritic cells absorb the cancer antigen. Now the dendritic cells are injected back into the patient. These now mature dendritic cells present the cancer antigen to helper and cytotoxic T cells. These immune cells now initiate an specific immune response to the cancer cells.

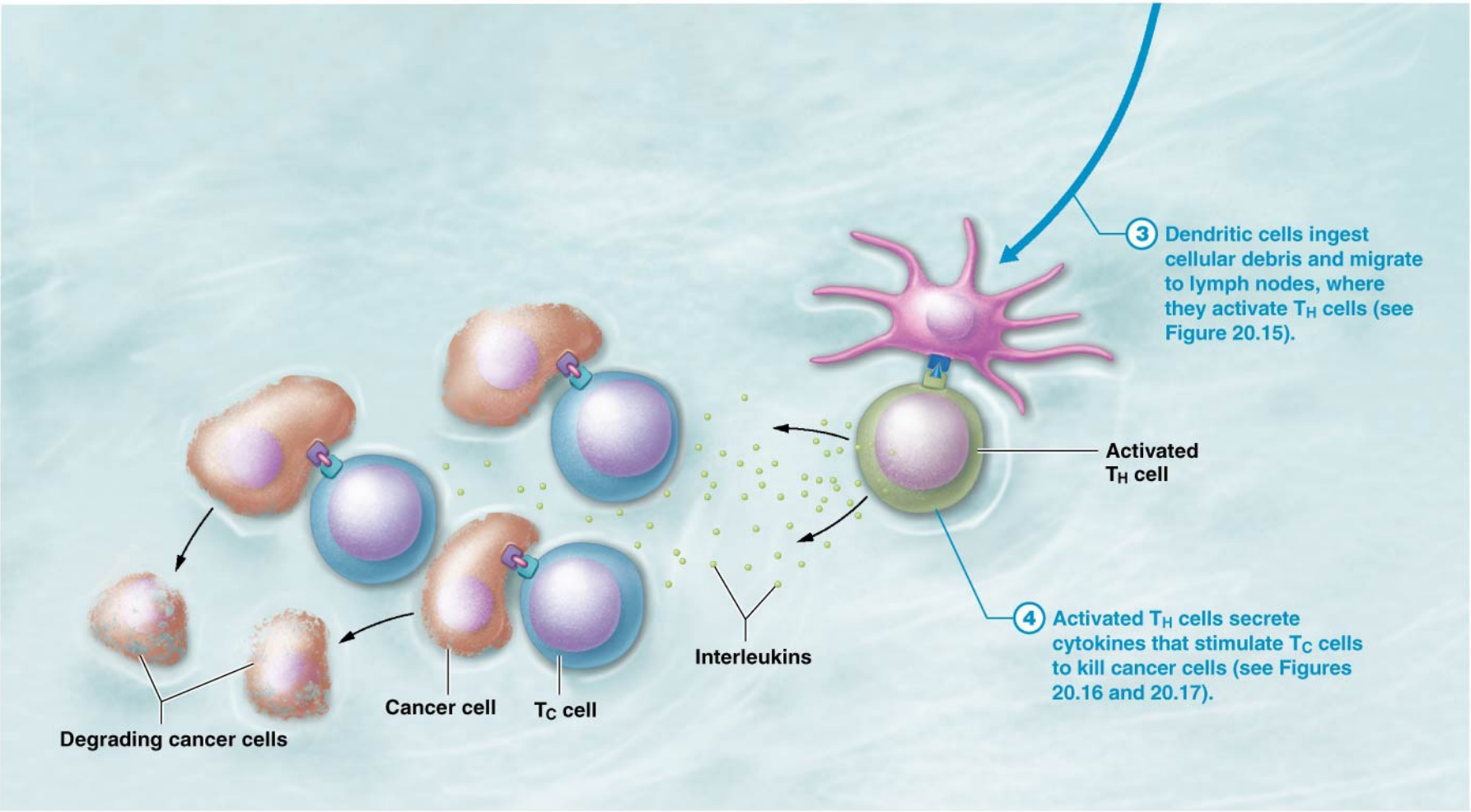
Dendritic Cell Vaccines



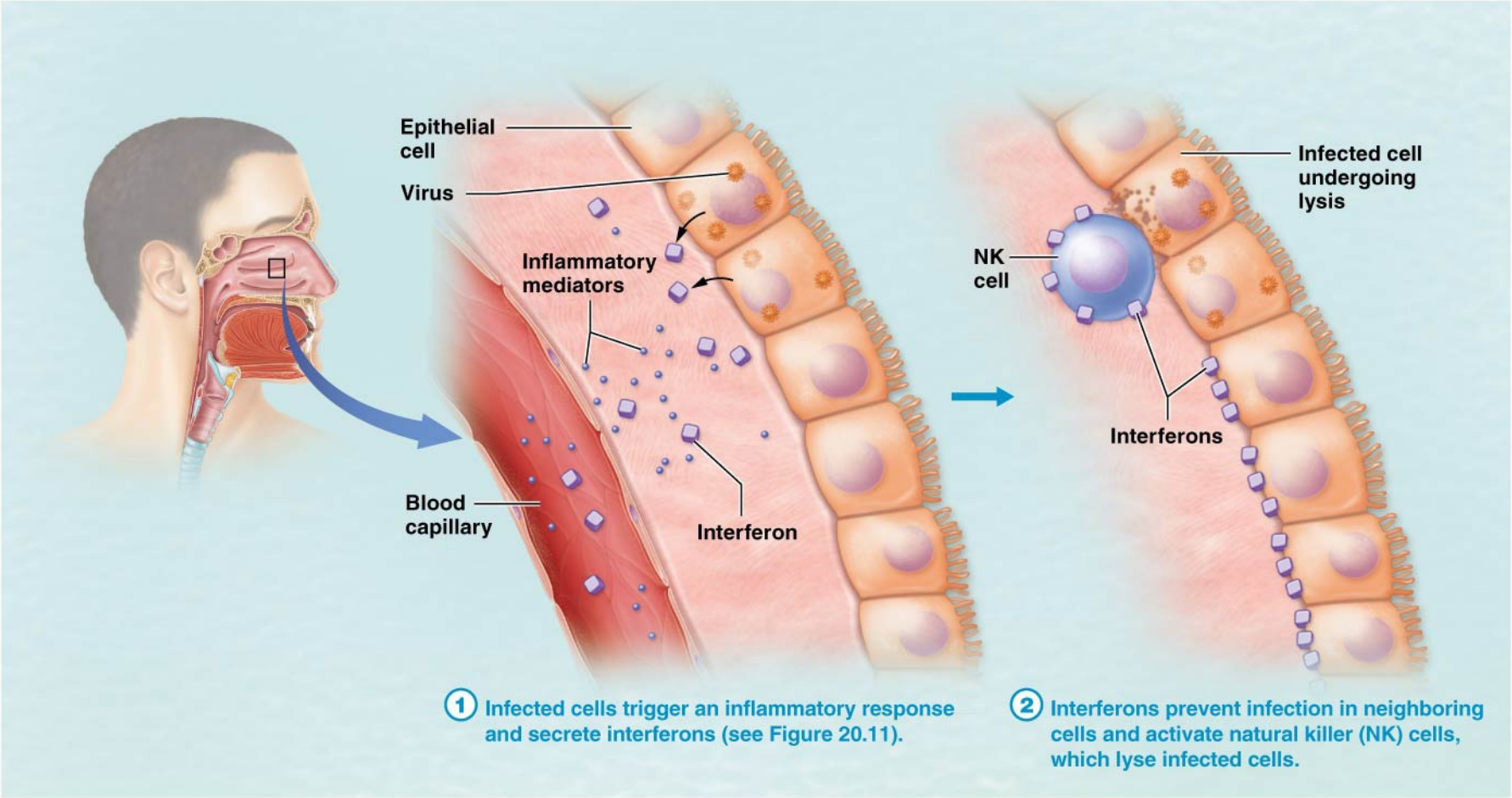
The Big Picture
Using the Immune Response to Cancer Cells. (slide 1 fo 2)



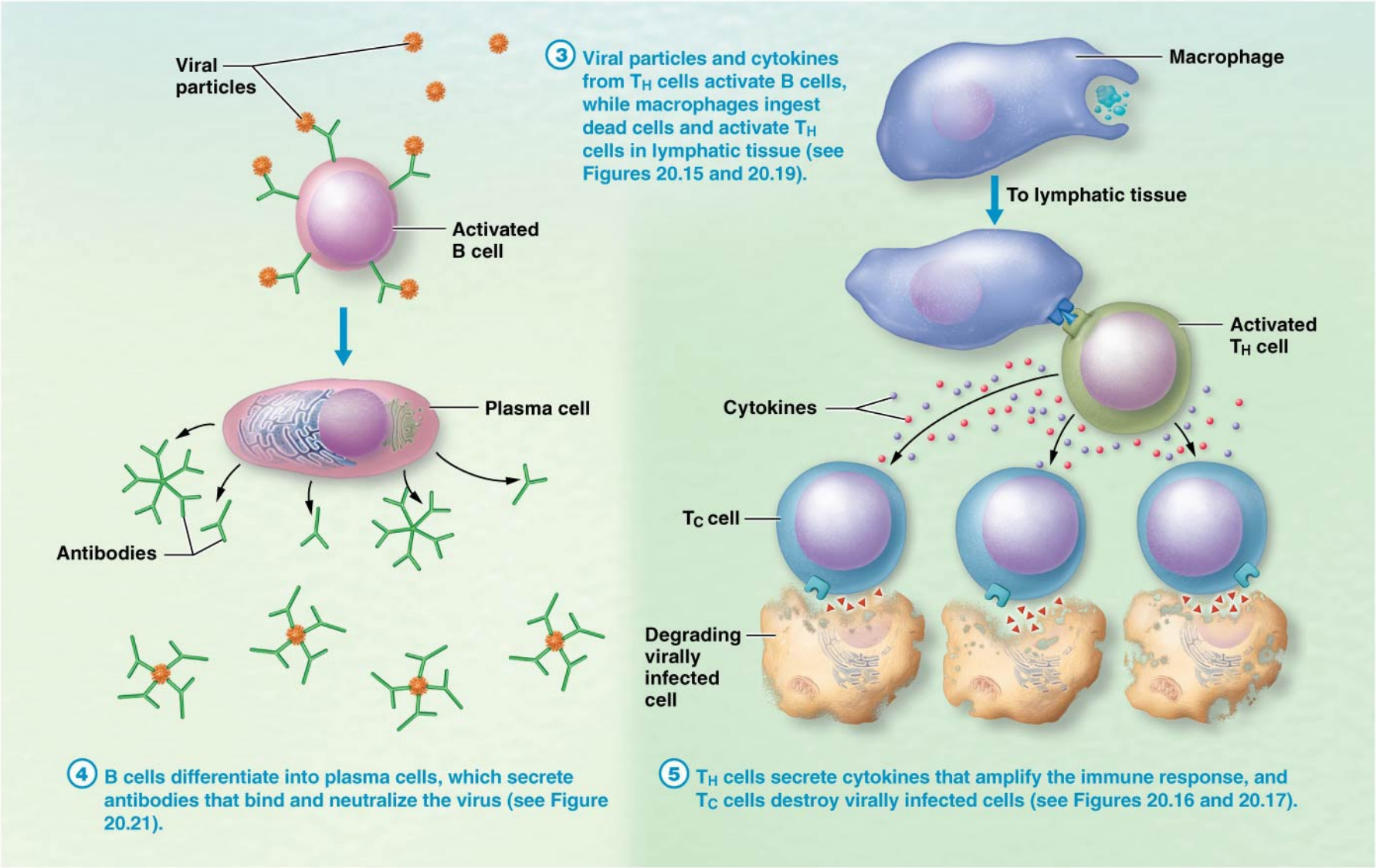
The Big Picture
Using the Immune Response to Cancer Cells. (slide 2 of 2)



The Big Picture
Immune Response to the Common Cold.
This is a viral infection. (slide 1 of 2)

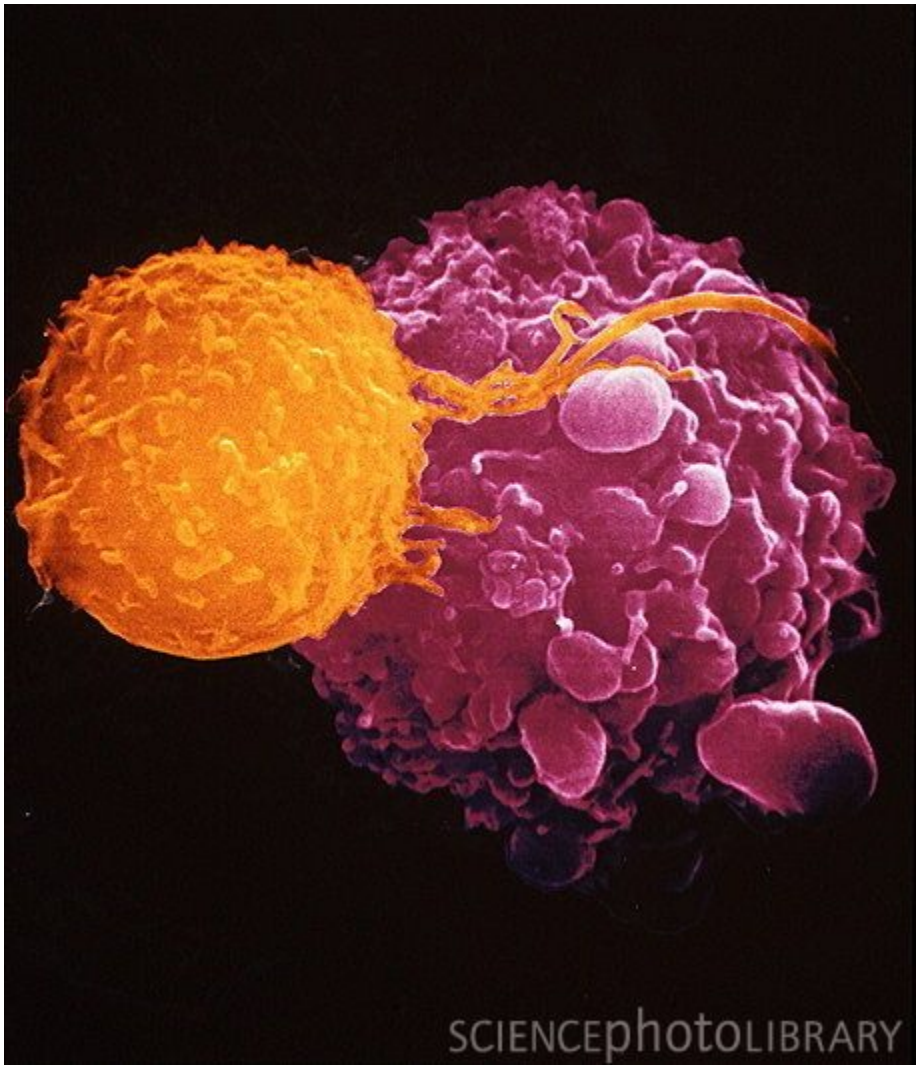


The Big Picture
Using the Immune Response to the Common Cold.
This is a viral infection. (slide 2 of 2)

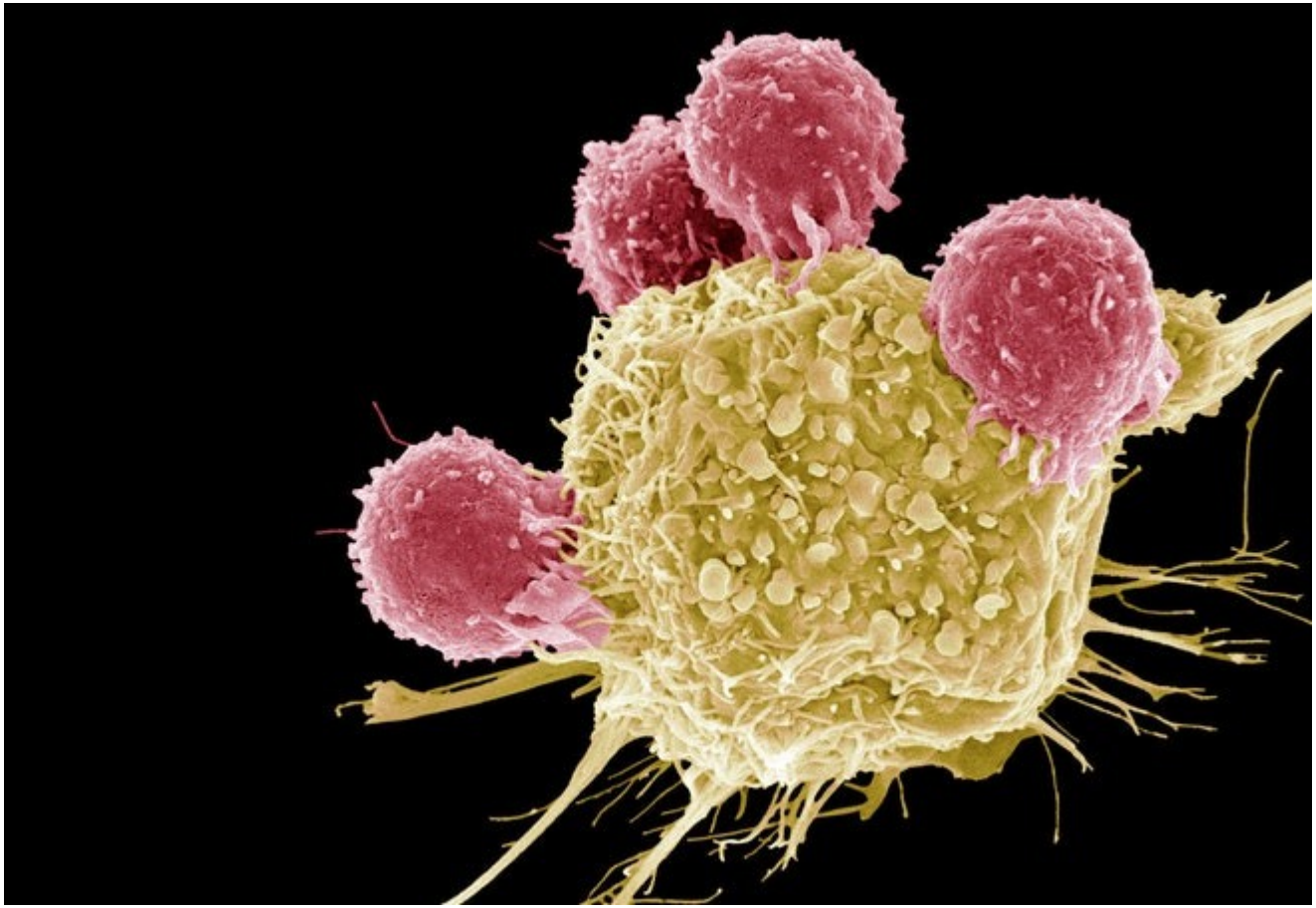


Immune system fighting a cancer cell.

A killer T-lymphocyte (orange) inducing a cancer cell to undergo Programmed Cell Death (apoptosis).



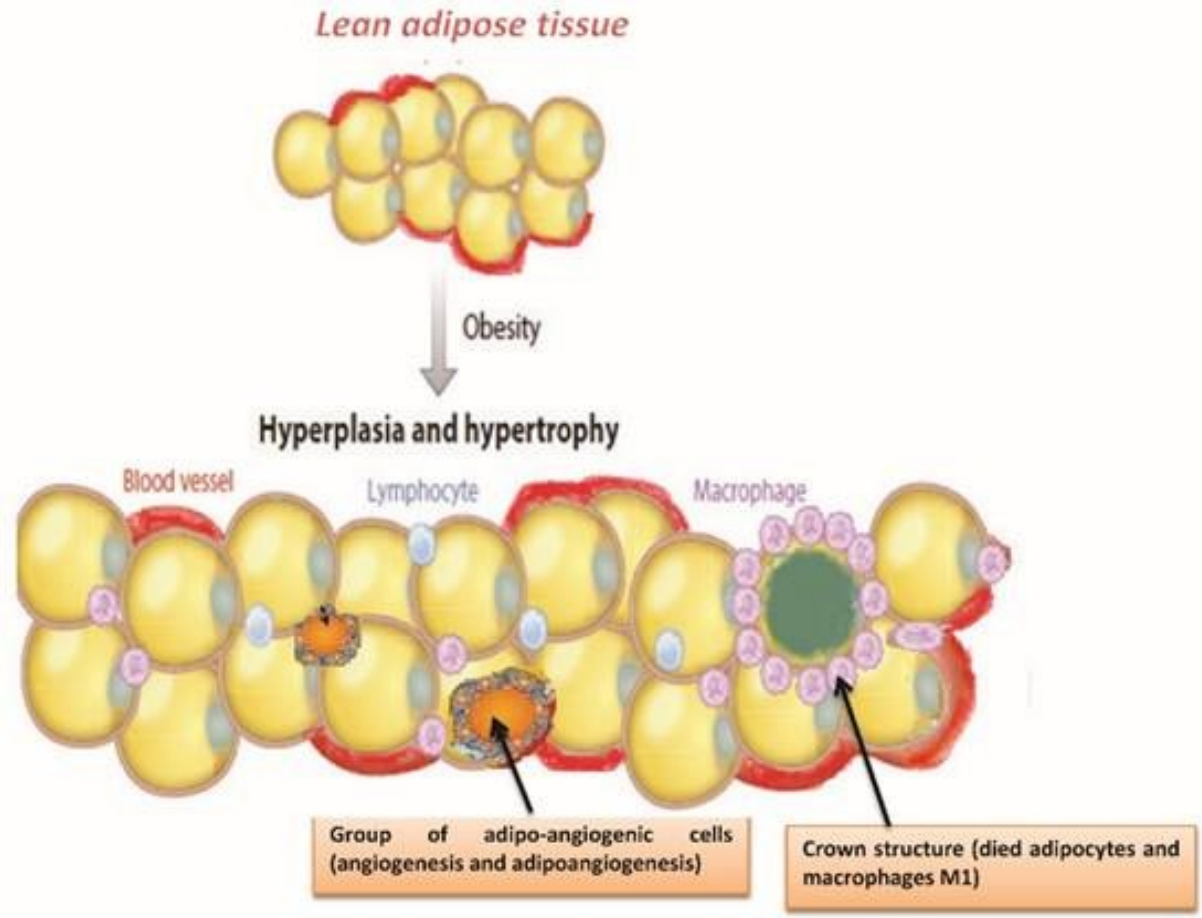
Coloured scanning electron micrograph of T cells (pink) attacking a cancer cell. Editing T cells' genes could soon enhance their cancer-attacking abilities.

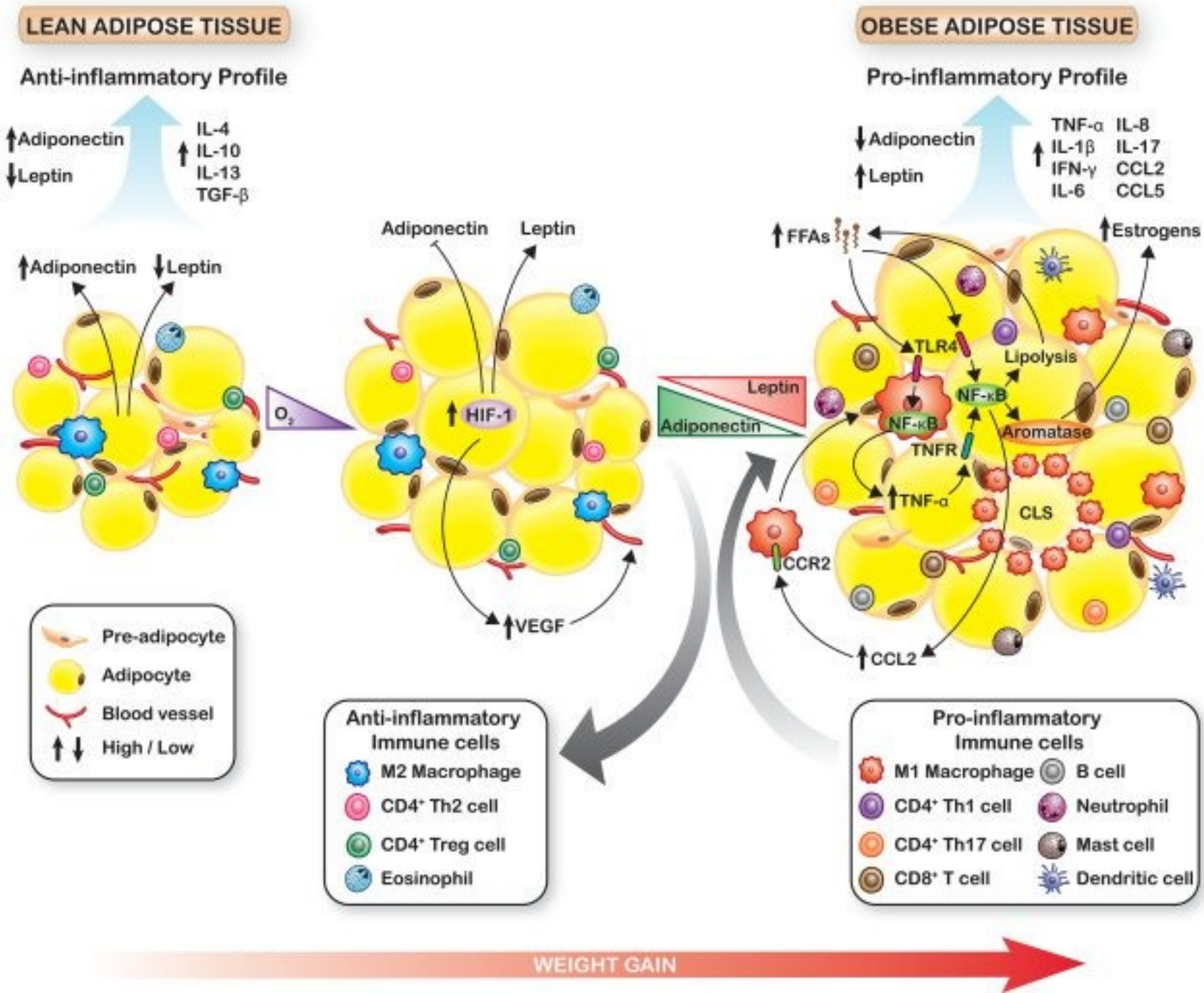


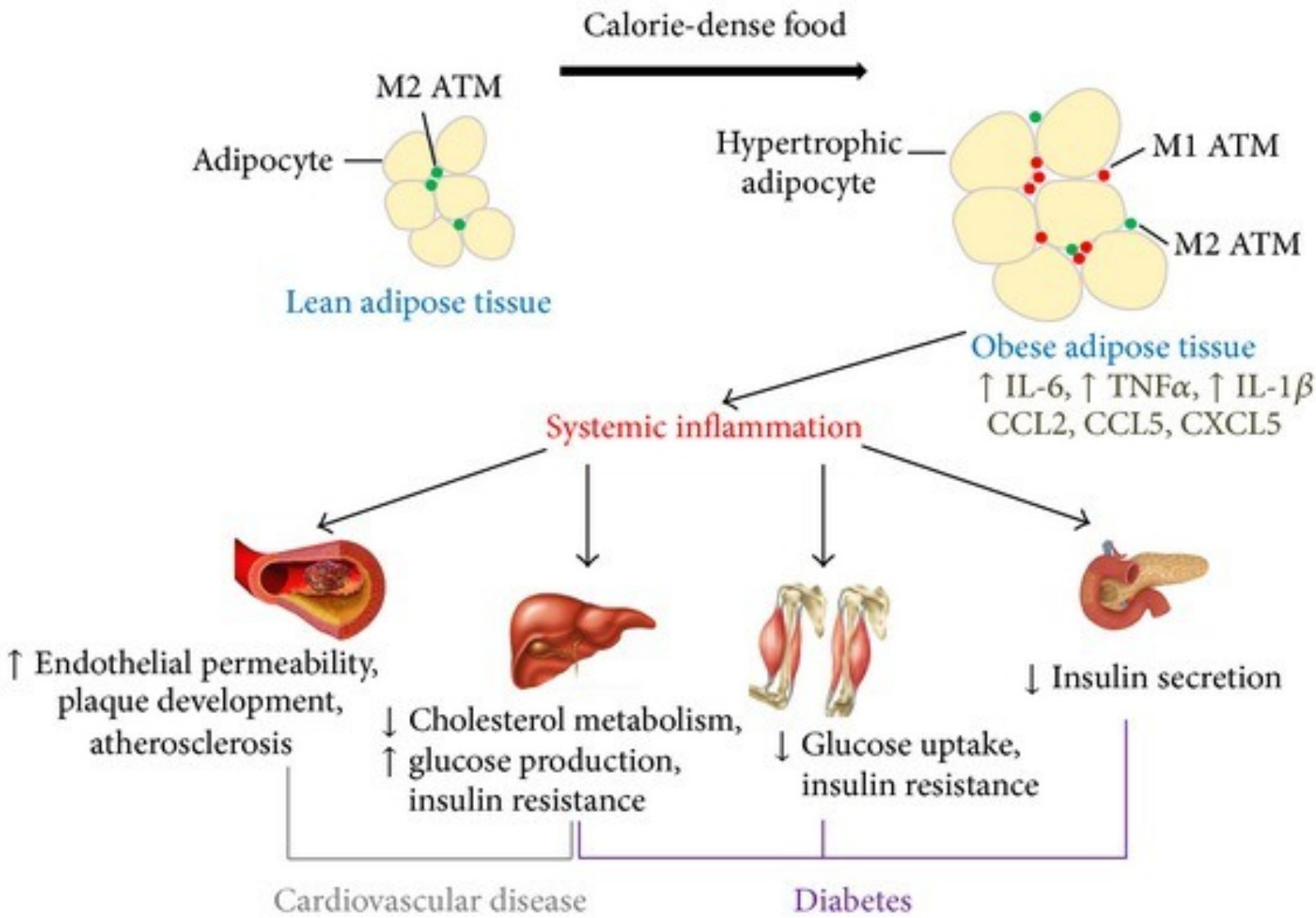
Obesity contributes to development of diabetes and cardiovascular disease. Adipose tissue is composed of two main cell types, adipocytes and stromovascular mononuclear cells (i.e., resident leukocytes).

Adipose tissue macrophages (ATMs) are the most frequent leukocyte subtype in fat tissues. Normal adipose tissue is populated with the alternatively activated M2 ATMs. Persistent or frequent consumption of calorie-dense food results in obesity that is associated with increased adiposity which includes adipose tissue hypertrophy and influx of proinflammatory monocytes that mature to classically activated M1 ATMs.

Obesity induces production of proinflammatory cytokines (i.e., IL-6, TNFα, and IL-1β) and several chemokines including CCL2, CCL5, and CXCL5 among others by adipocytes and immune cells trigger adipose tissue inflammation, which when prolonged progresses to systemic inflammation that affects (i) vasculature increasing permeability of endothelium, thereby triggering plaque development and cardiovascular disease; (ii) anabolic actions of insulin and insulin signaling in metabolic tissues including liver and skeletal muscle, causing insulin resistance that manifests as impaired glucose disposal in muscle and altered cholesterol and glucose metabolism in the liver, which in turn triggers hyperinsulinemia, hyperglycemia, and hyperlipidemia that all contribute to type 2 diabetes and cardiovascular disease; and (iii) pancreas, decreasing insulin secretion that leads to hyperglycemia, which is a hallmark of diabetes.


Lean adipose tissue
Obesity
Hyperplasia and hypertrophy
Blood vessel
Lymphocyte
Macrophage
Group of adipo-angiogenic cells (angiogenesis and adipoangiogenesis)
Crown structure (died adipocytes and macrophages M1)


LEAN ADIPOSE TISSUE
Anti-inflammatory Profile
↑Adiponectin
↓Leptin
IL-4
↑ IL-10
IL-13
TGF-β
↑Adiponectin ↓Leptin
O2
Adiponectin
Leptin
↑HIF-1
↑VEGF
Leptin
Adiponectin
OBESE ADIPOSE TISSUE
Pro-inflammatory Profile
↓Adiponectin
↑Leptin
TNF-α IL-8
↑ IL-1β IL-17
IFN-γ CCL2
IL-6 CCL5
↑FFAs
↑Estrogens
TLR4
Lipolysis
NF-κB
NF-κB
Aromatase
TNFR
↑TNF-α
CLS
CCR2
↑CCL2
Pre-adipocyte
Adipocyte
Blood vessel
↑↓ High / Low
Anti-inflammatory Immune cells
M2 Macrophage
CD4+ Th2 cell
CD4+ Treg cell
Eosinophil
Pro-inflammatory Immune cells
M1 Macrophage
B cell
CD4+ Th1 cell
Neutrophil
CD4+ Th17 cell
Mast cell
CD8+ T cell
Dendritic cell
WEIGHT GAIN


Calorie-dense food
M2 ATM
Adipocyte
Lean adipose tissue
Hypertrophic adipocyte
M1 ATM
M2 ATM
Obese adipose tissue
↑ IL-6, ↑ TNFα, ↑ IL-1β
CCL2, CCL5, CXCL5
Systemic inflammation
↑ Endothelial permeability, plaque development, atherosclerosis
↓ Cholesterol metabolism, ↑ glucose production, insulin resistance
↓ Glucose uptake, insulin resistance
↓ Insulin secretion
Cardiovascular disease
Diabetes