Series of lectures on different aspects of the Immune System for those interested in more detail (about 20 mins each lecture)

- Introduction to the Immune system: https://www.youtube.com/watch?v=bW-eEBxJYaM
- Leucocytes of the immune system: https://www.youtube.com/watch?v=ZQSzIOMRZMQ
- The innate immune system: https://www.youtube.com/watch?v=os1oh8AprYw
- The adaptive immune system: https://www.youtube.com/watch?v=Kr9WsHUSnp4
- The innate and adaptive immune systems: https://www.youtube.com/watch?v=e2TCjFPn2g8
- Antigen presenting cells: https://www.youtube.com/watch?v=TadJkUCJLHo
- Activation of lymphocytes: https://www.youtube.com/watch?v=Dvs1lN_uKXc
- Mechanism of B lymphocytes: https://www.youtube.com/watch?v=pZLDjmfaJ0Y
- Major histocompatibility complex: https://www.youtube.com/watch?v=yDAGxVxY-L8
- The Complement System: https://www.youtube.com/watch?v=ER0hzqJnt_s

The Body Works? (3):

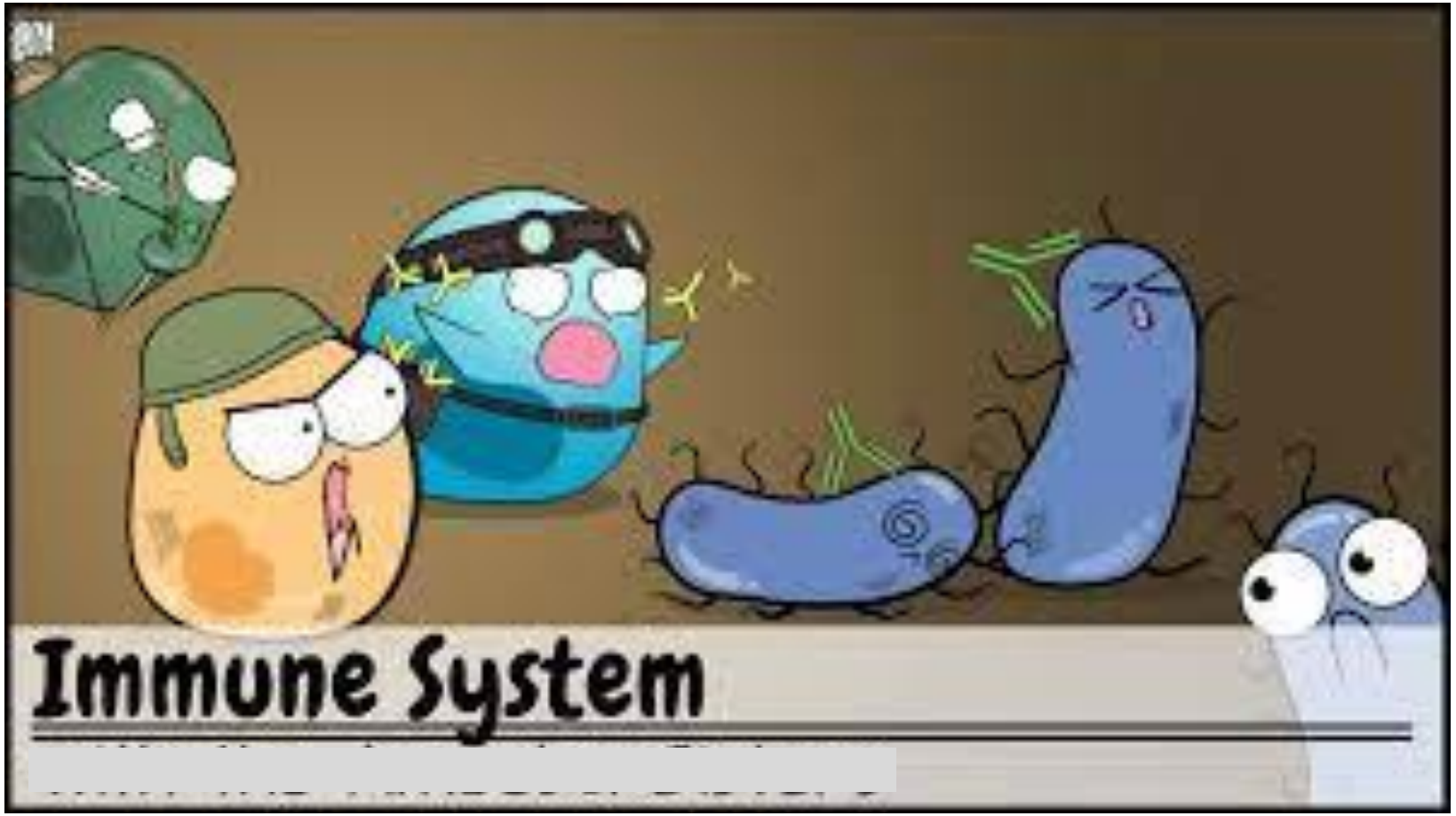
- The Heart (March 5th)
- The Articulations, in particular the knee and hip joints (March 12th)
- The Brain (March 19th)
- ***The Immune System (March 26th)***

The Body Works?

- **Presenters:**
  - *David Docherty, PhD*
    - Professor Emeritus, School of Exercise Science, Physical and Health Education, University of Victoria, B.C.
  - *Chris Pengilly, M.D.*
    - Retired Family Physician and frequent contributor to the Times Colonist on medical matters.

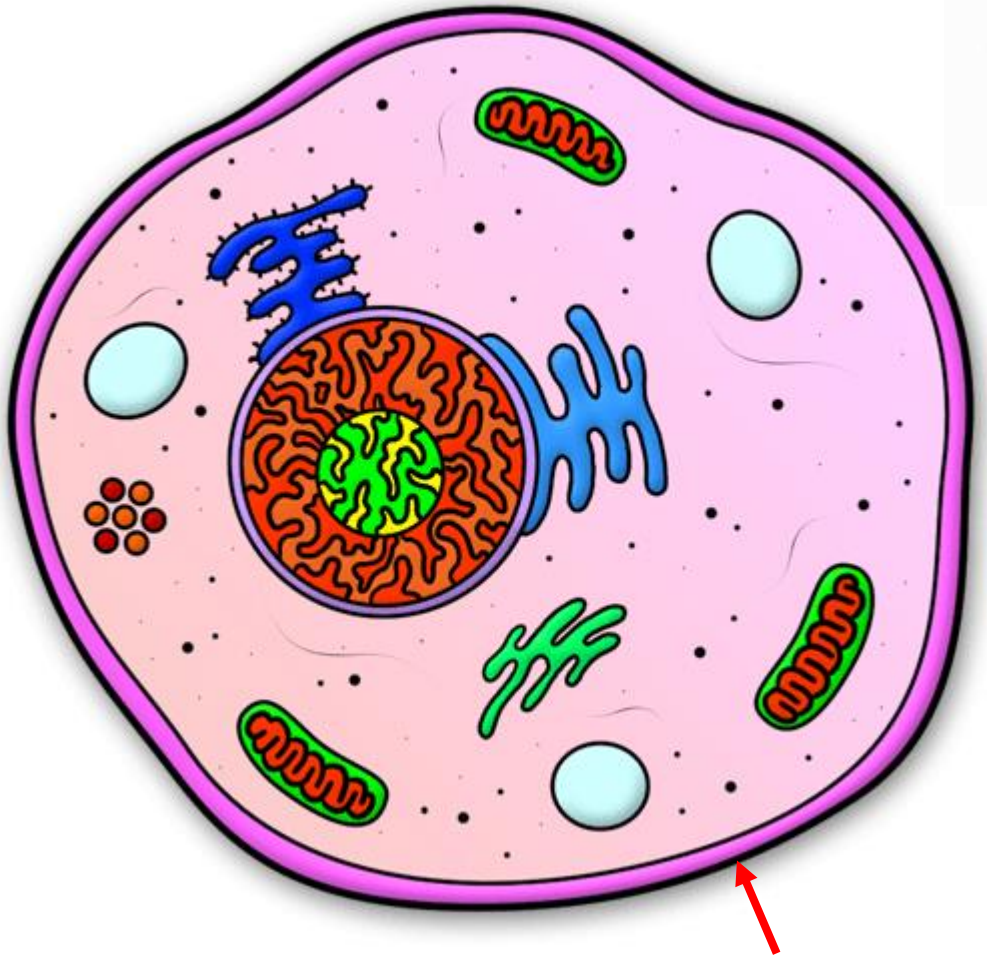
Disclaimer:

- I do not profess to be an expert on the immune system
- However, it is something I have always been interested in learning more about and the pandemic has provided that opportunity
- I have taught anatomy and physiology for many years and have always been amazed and fascinated with how the body works
- So thank you for the opportunity to keep on learning and expanding what I know



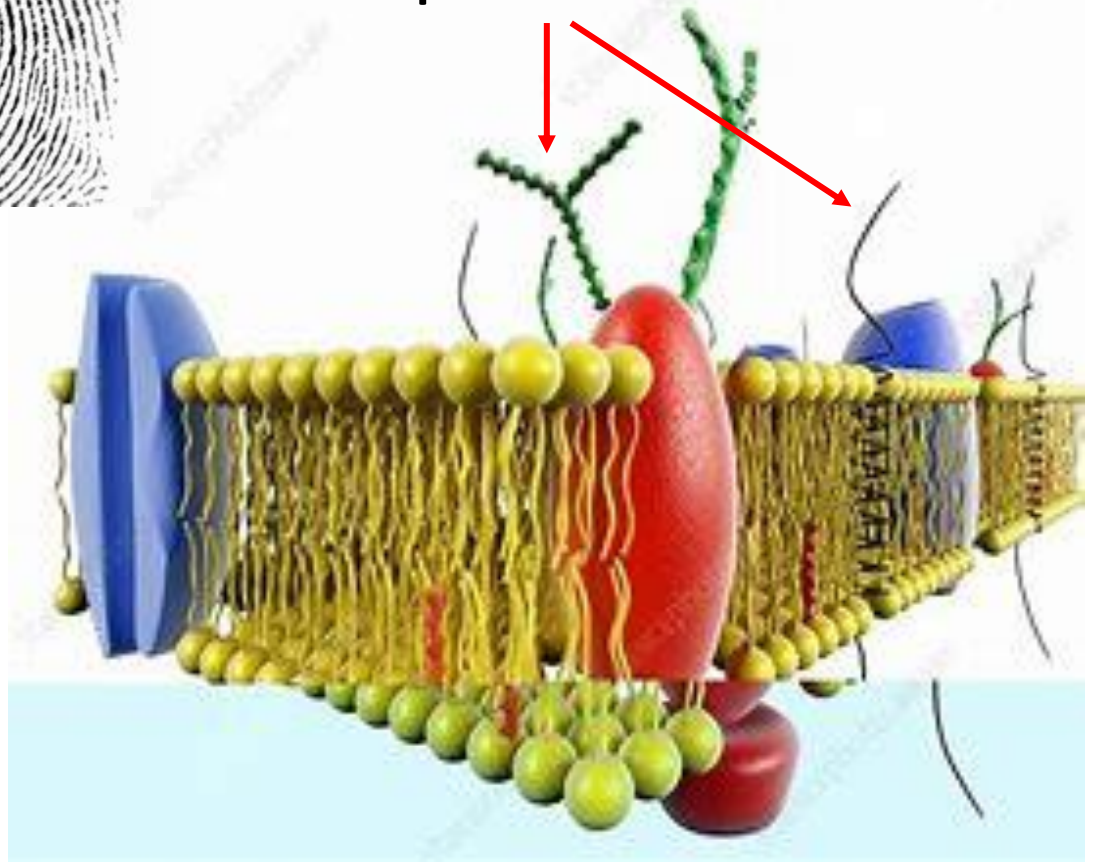
A bit about the immune system: *Designed to attack anything the body doesn't recognize as belonging!*

Typical human cell

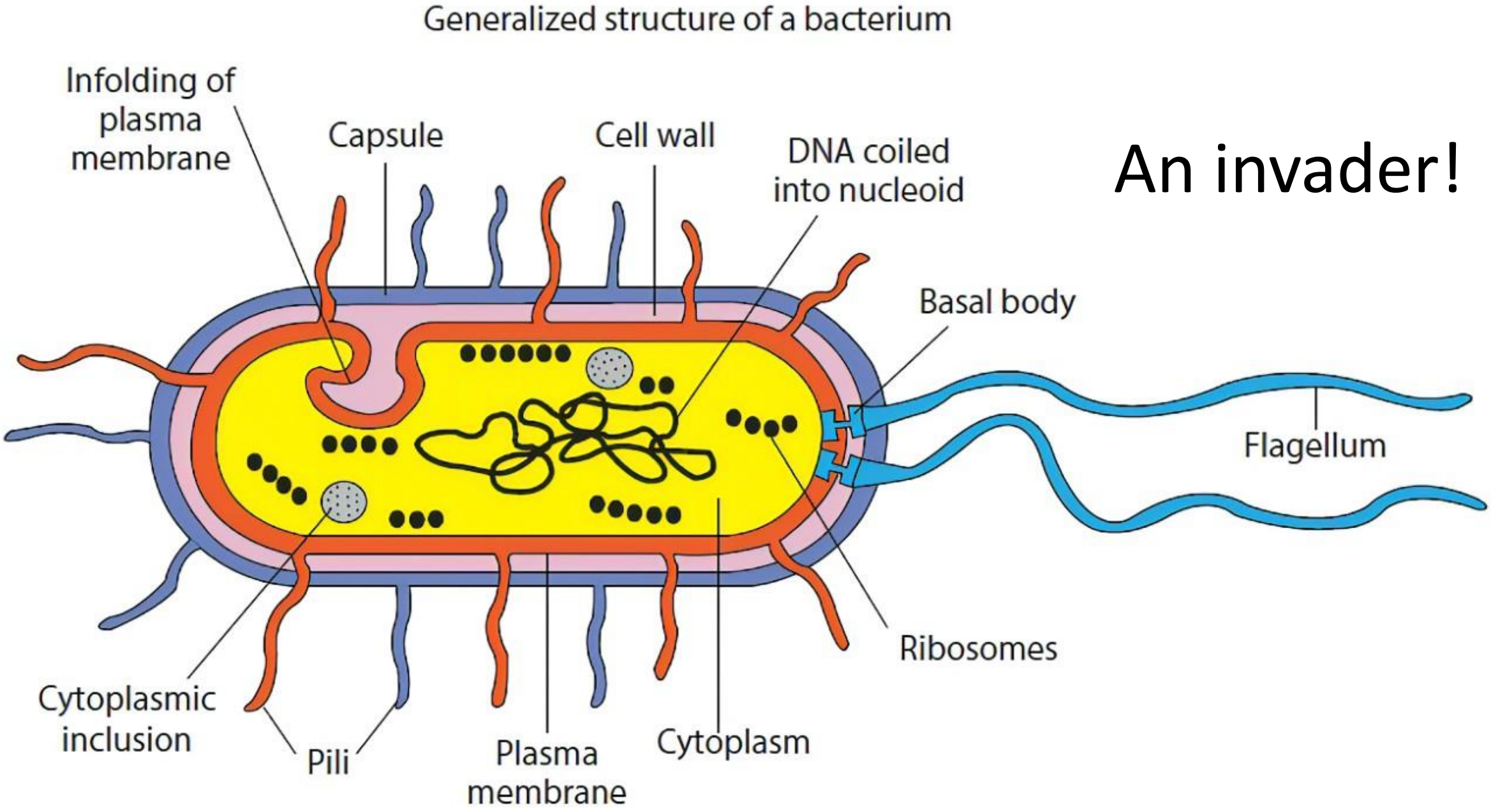


Cell membrane

Unique cell markers

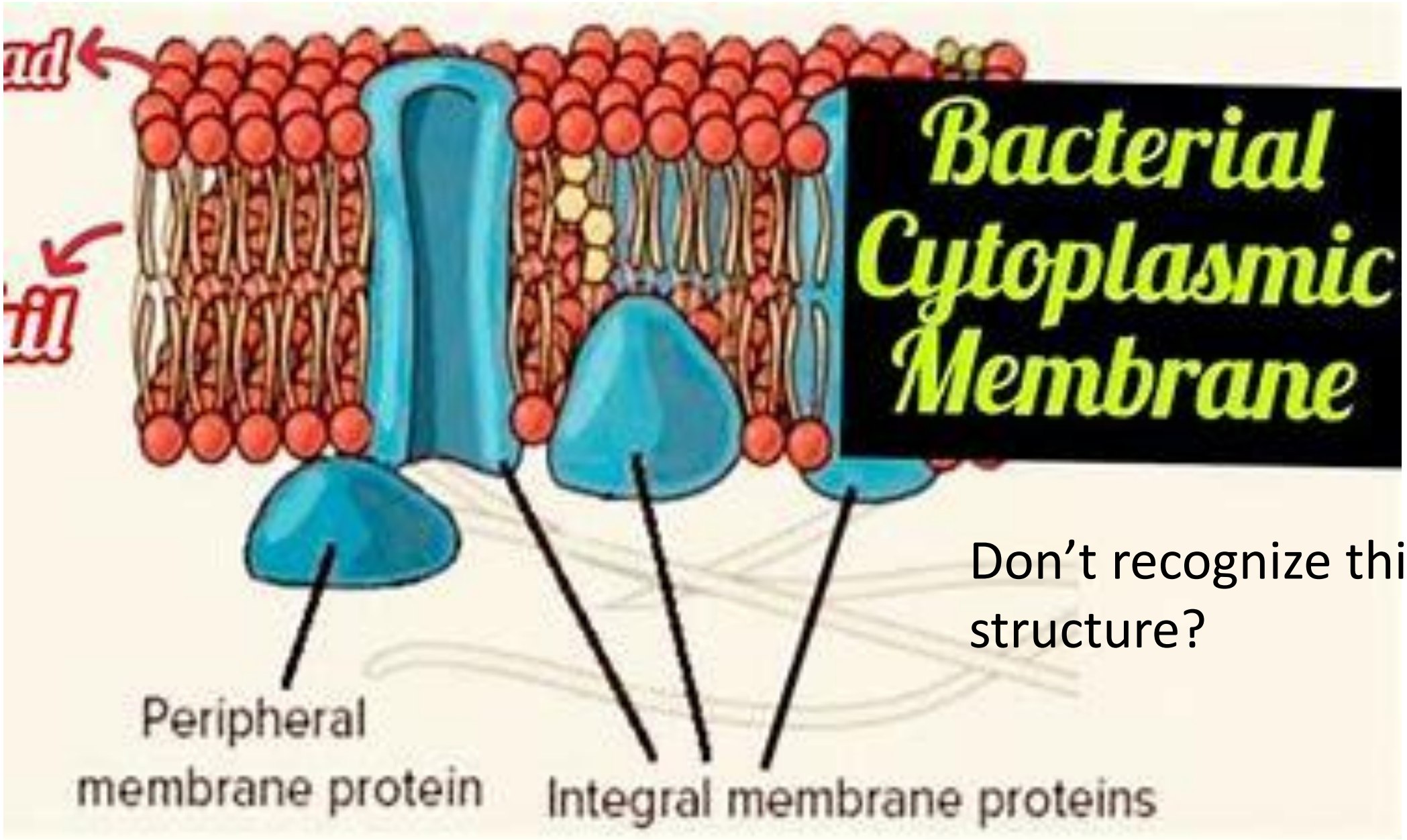


Close up of cell membrane



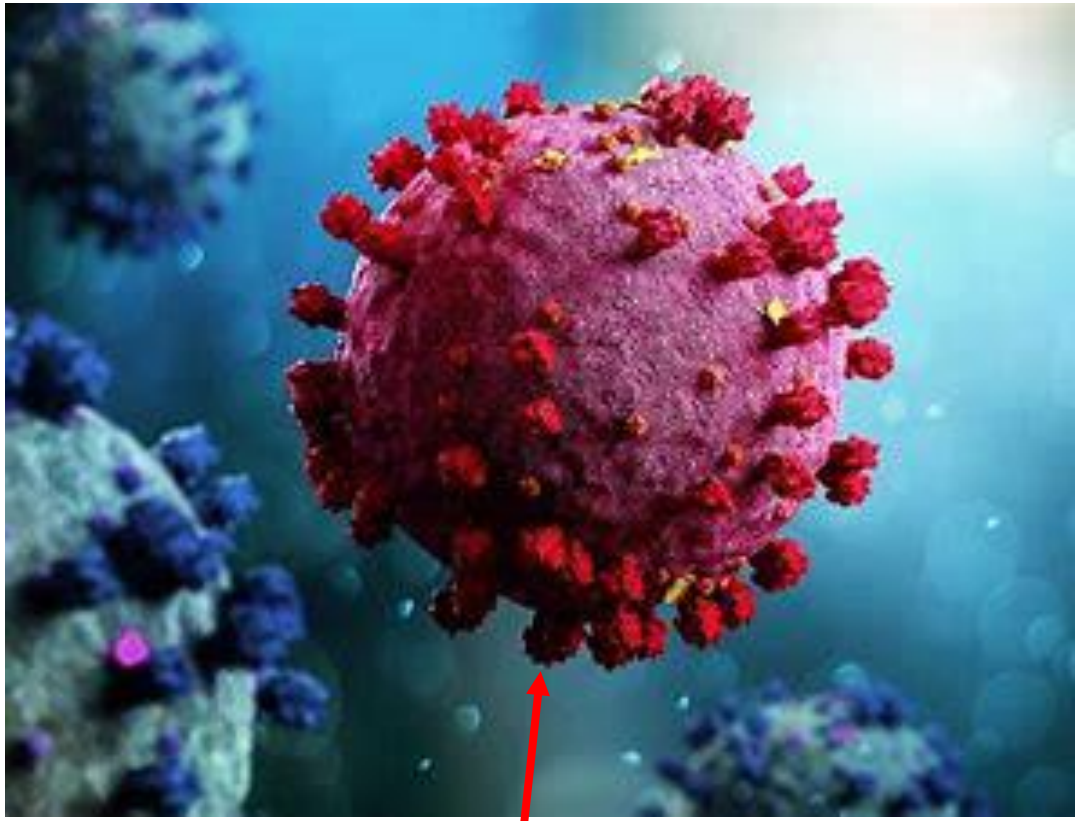
An invader!

Figure 7.1: Generalized structure of a bacterium

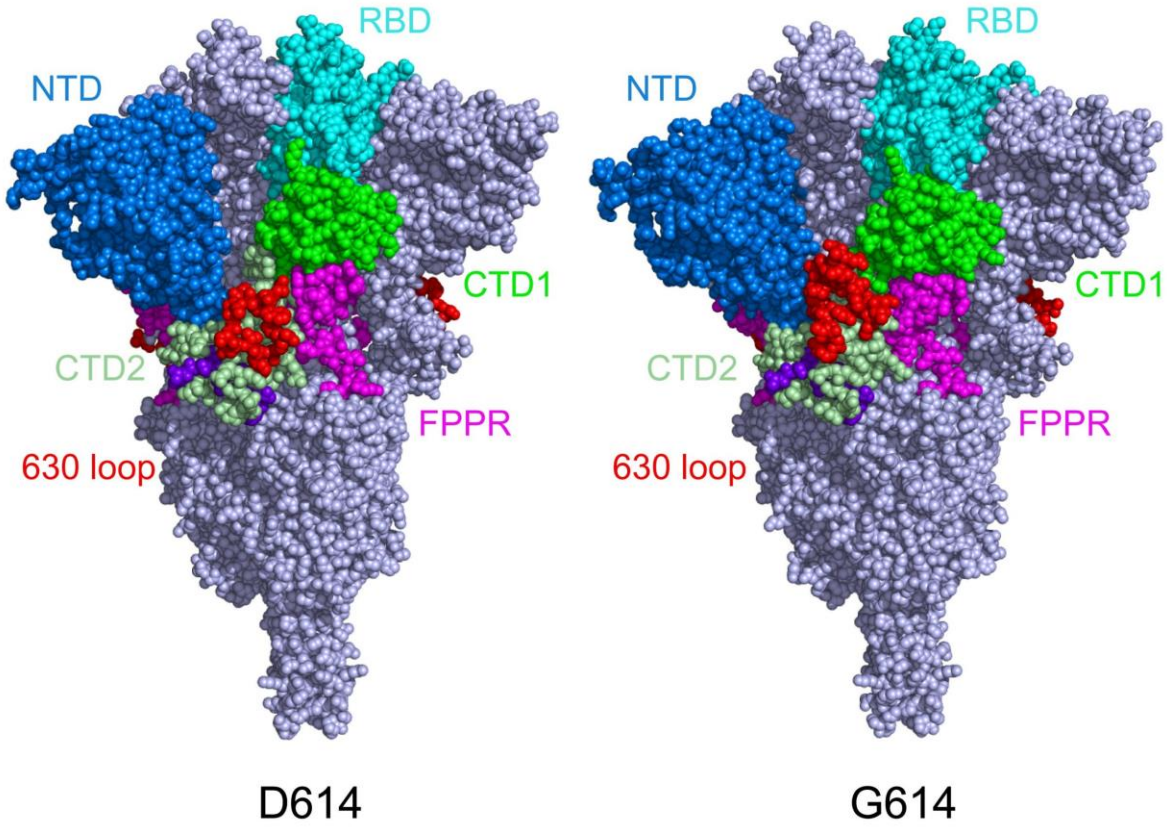


Don’t recognize this structure?

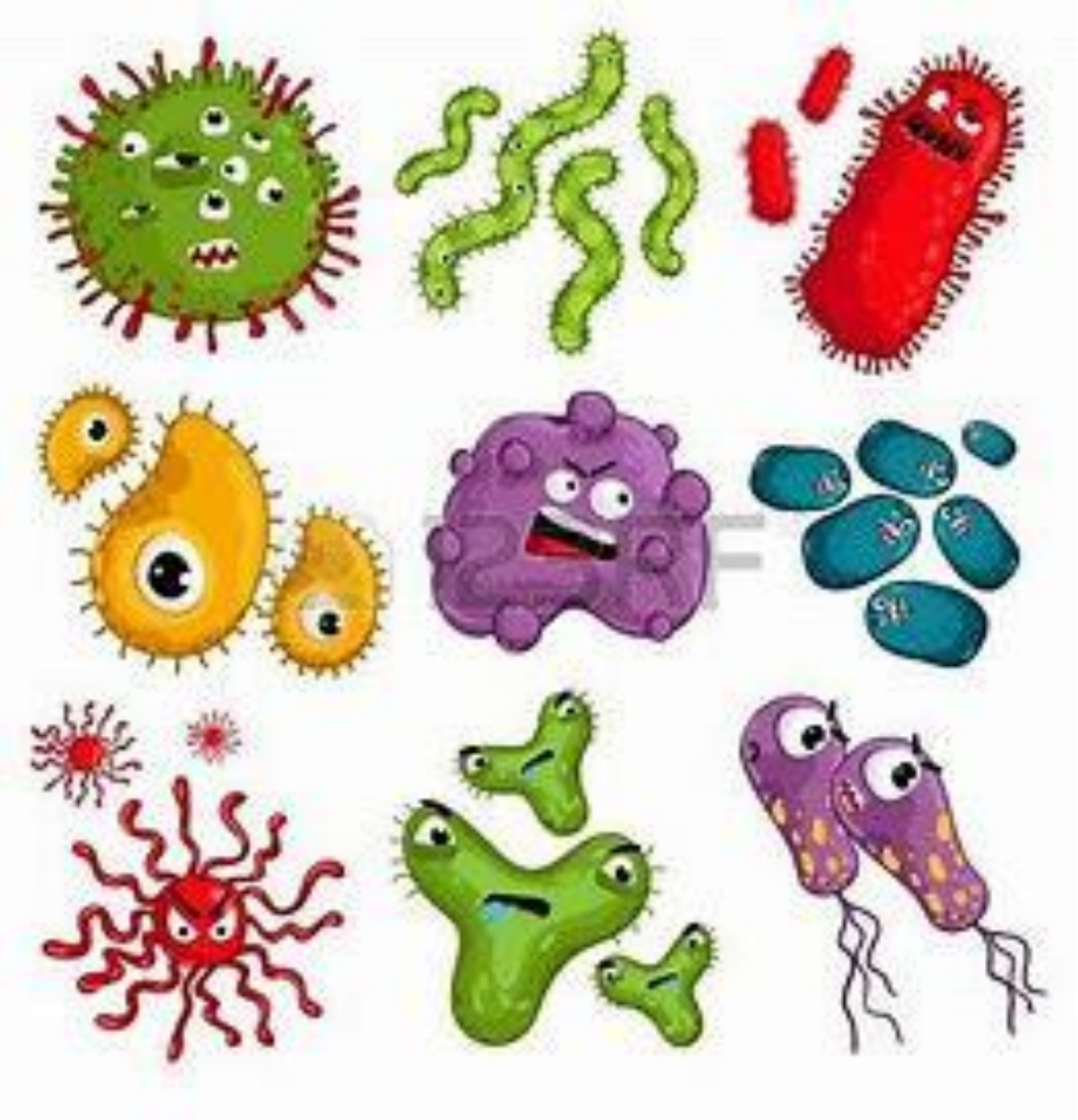
Another invader! COVID 19



The spike protein



Complexity of spike protein -variants



Pathogen: something that has potential to cause disease or sickness

Types of pathogens:

Bacteria

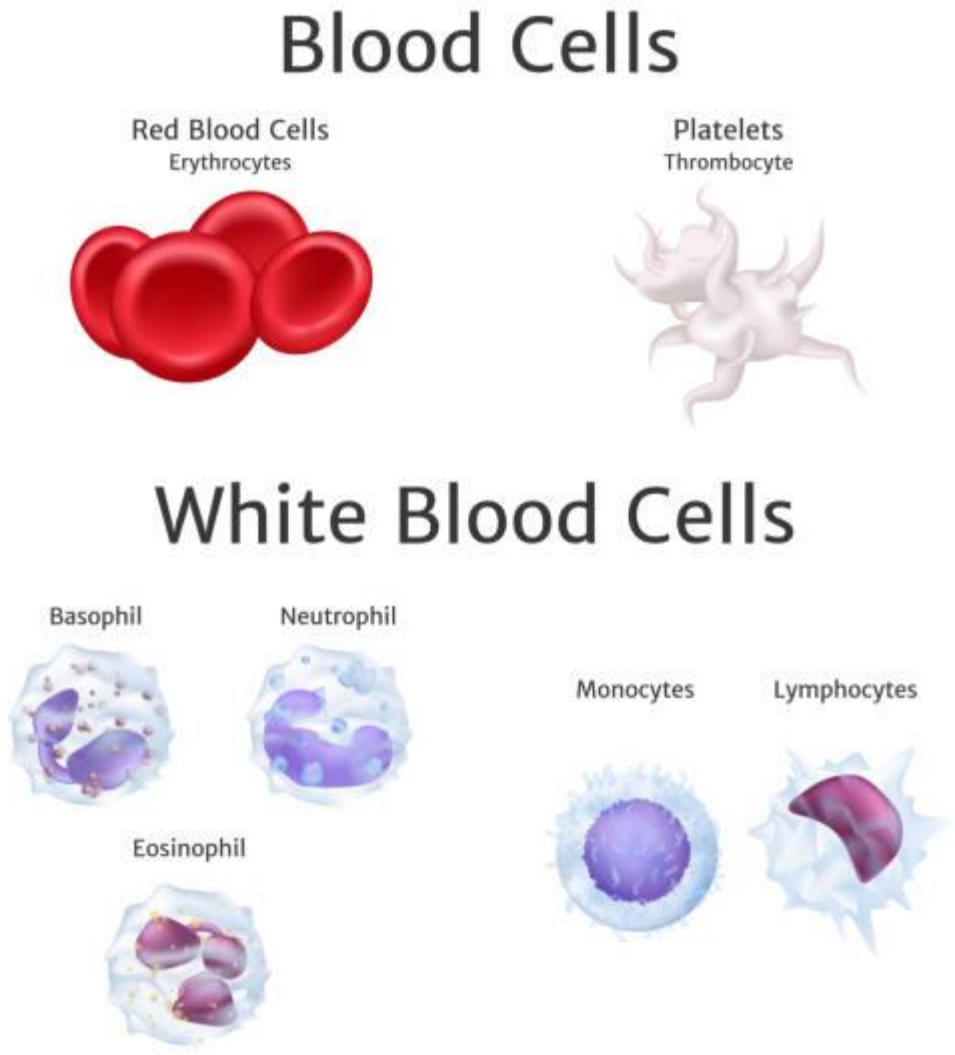
Fungi

Parasites

Toxins

Viruses

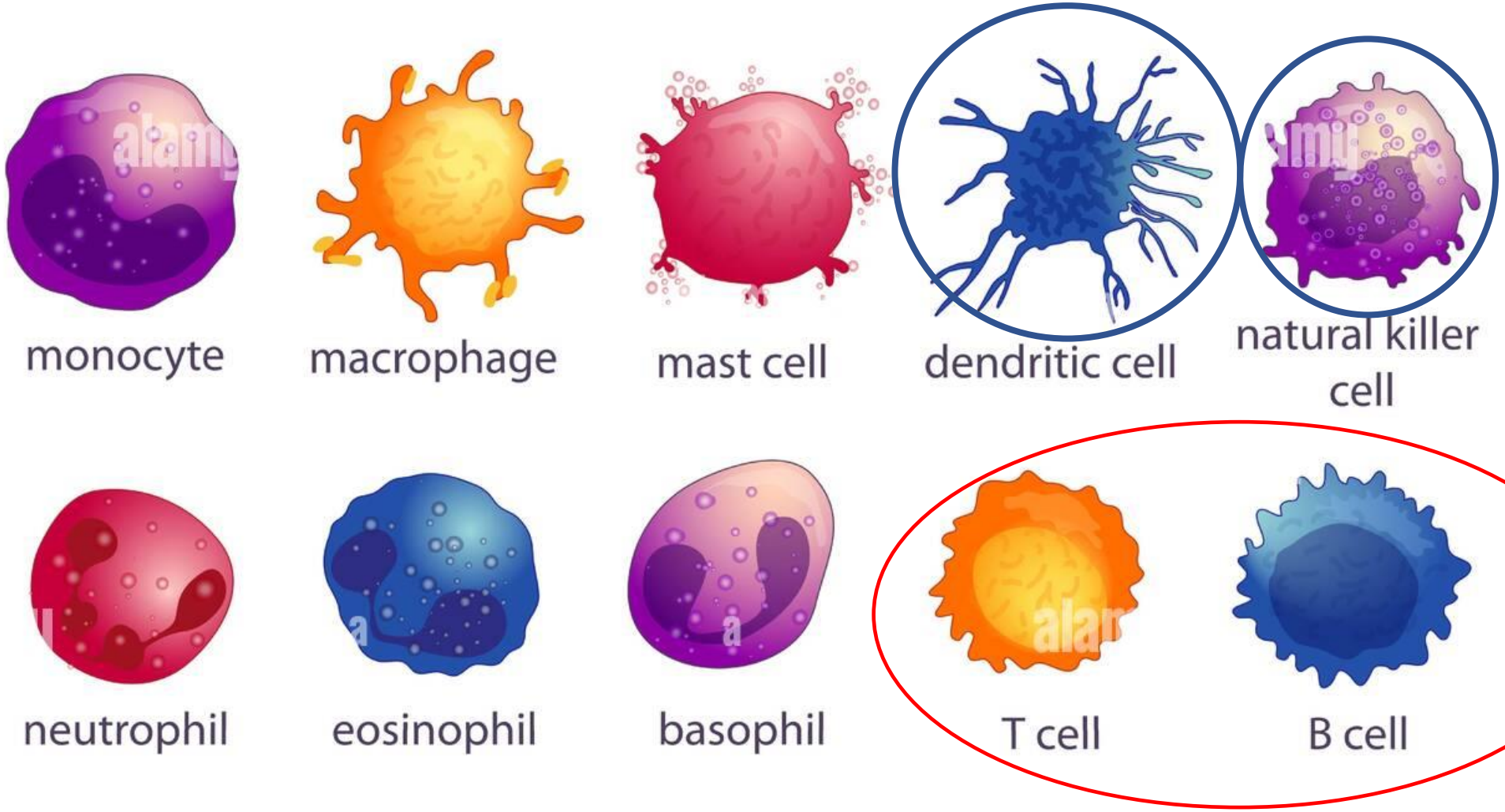
The body is very effective in fighting off invaders! Don't mess with me ☺



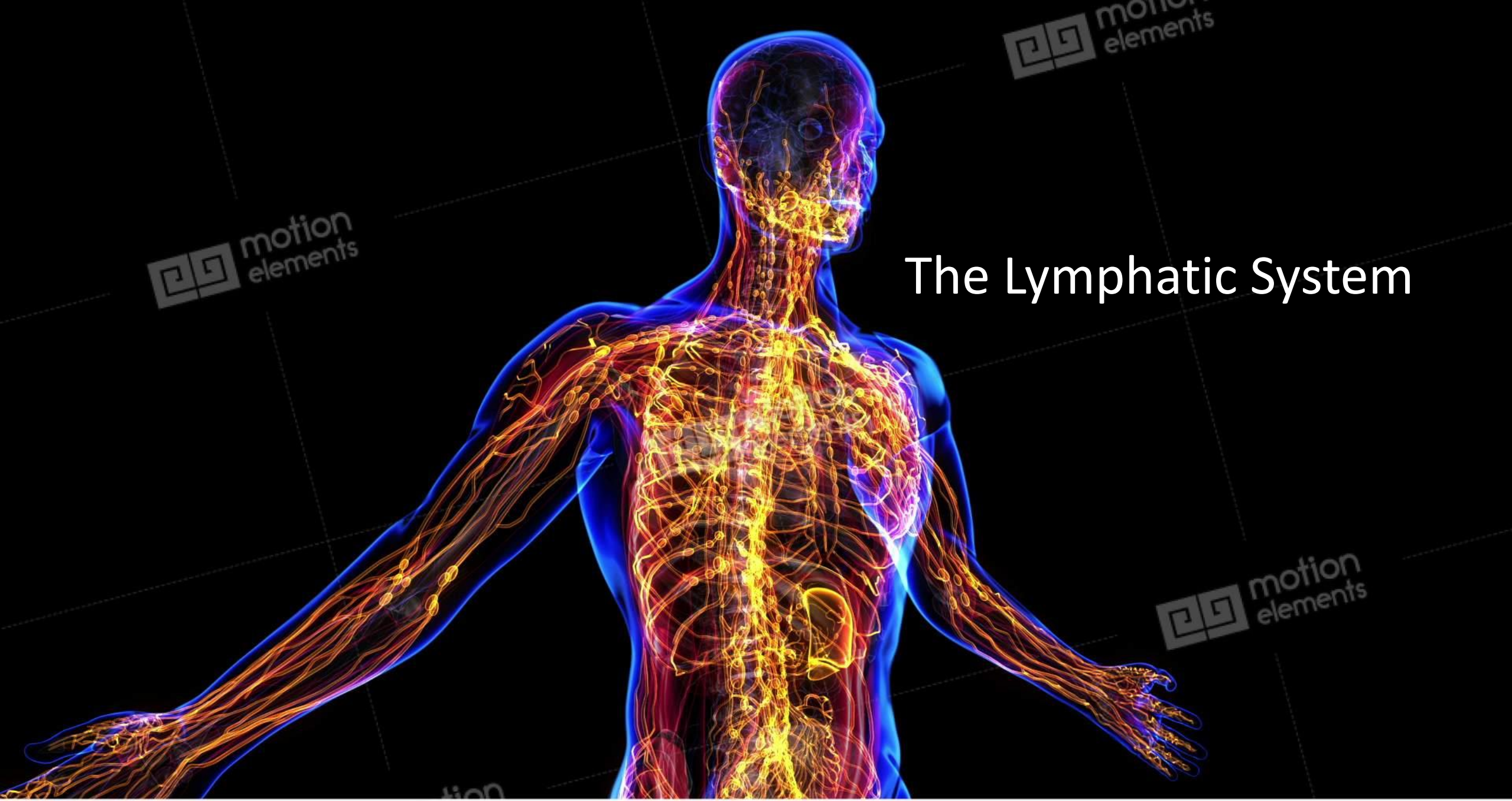
So how does it do it?

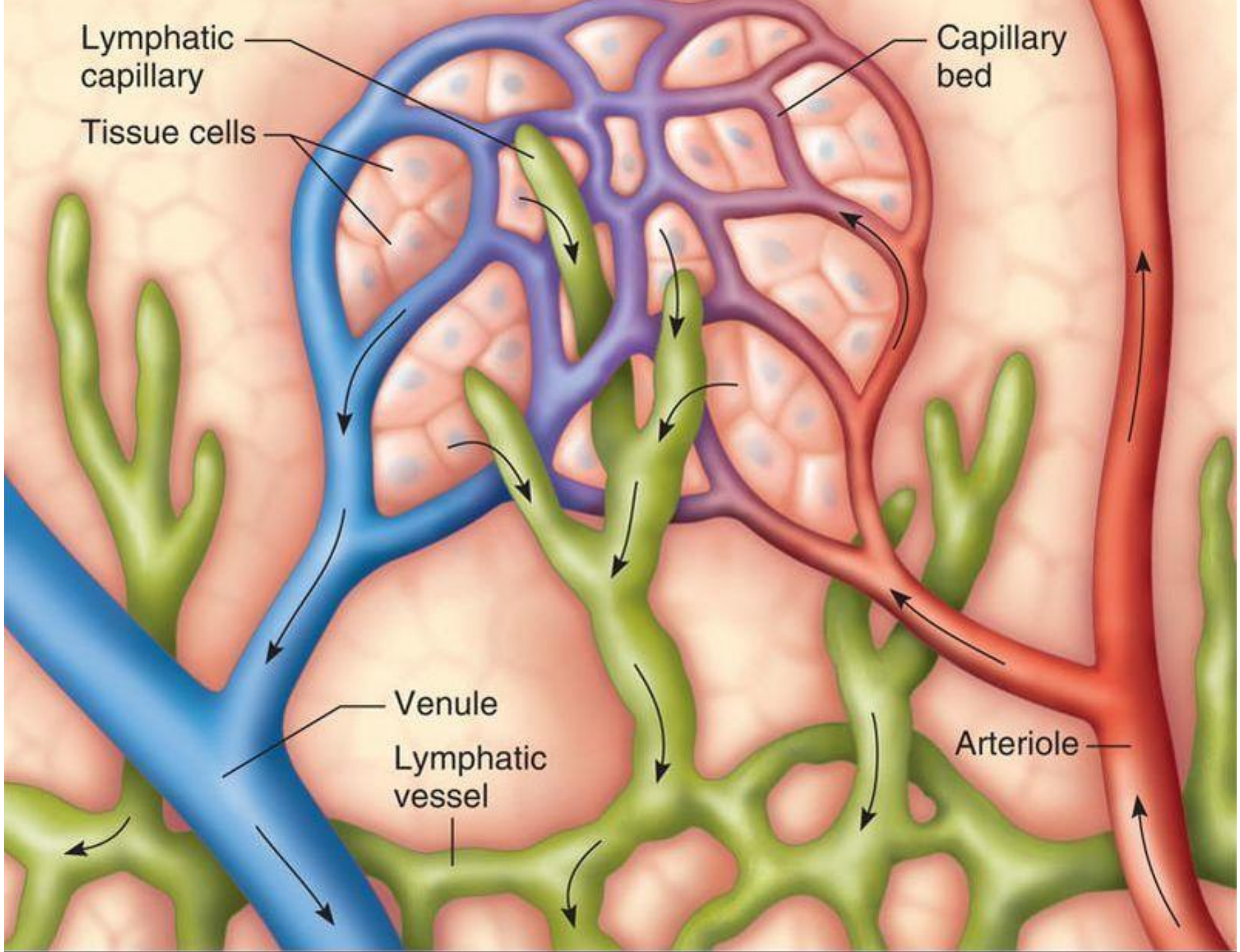
It really is amazing but also very complicated!

IMMUNE SYSTEM CELLS

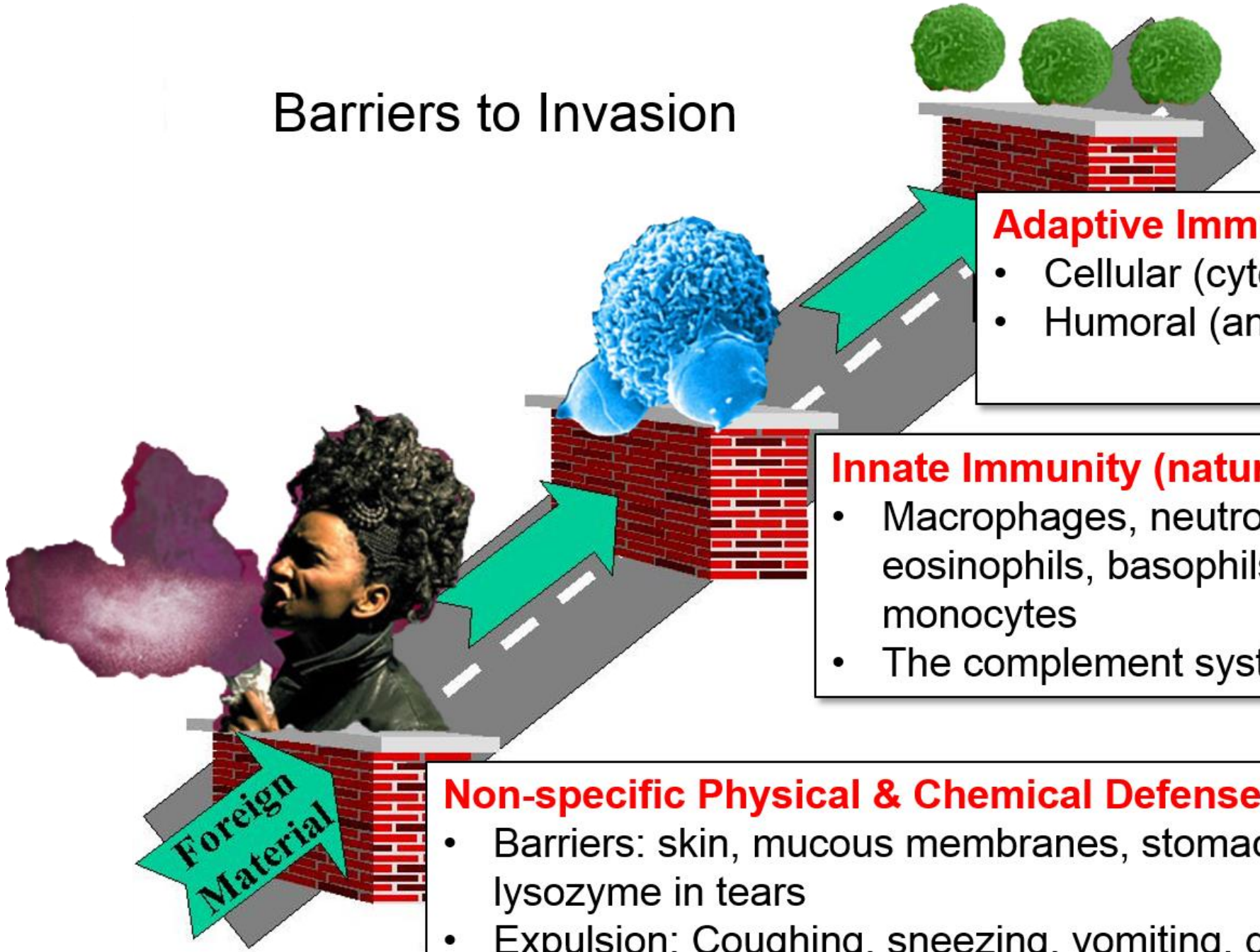


The Circulatory System




Lymphatic capillary
Tissue cells
Capillary bed
Venule
Lymphatic vessel
Arteriole

Barriers to Invasion

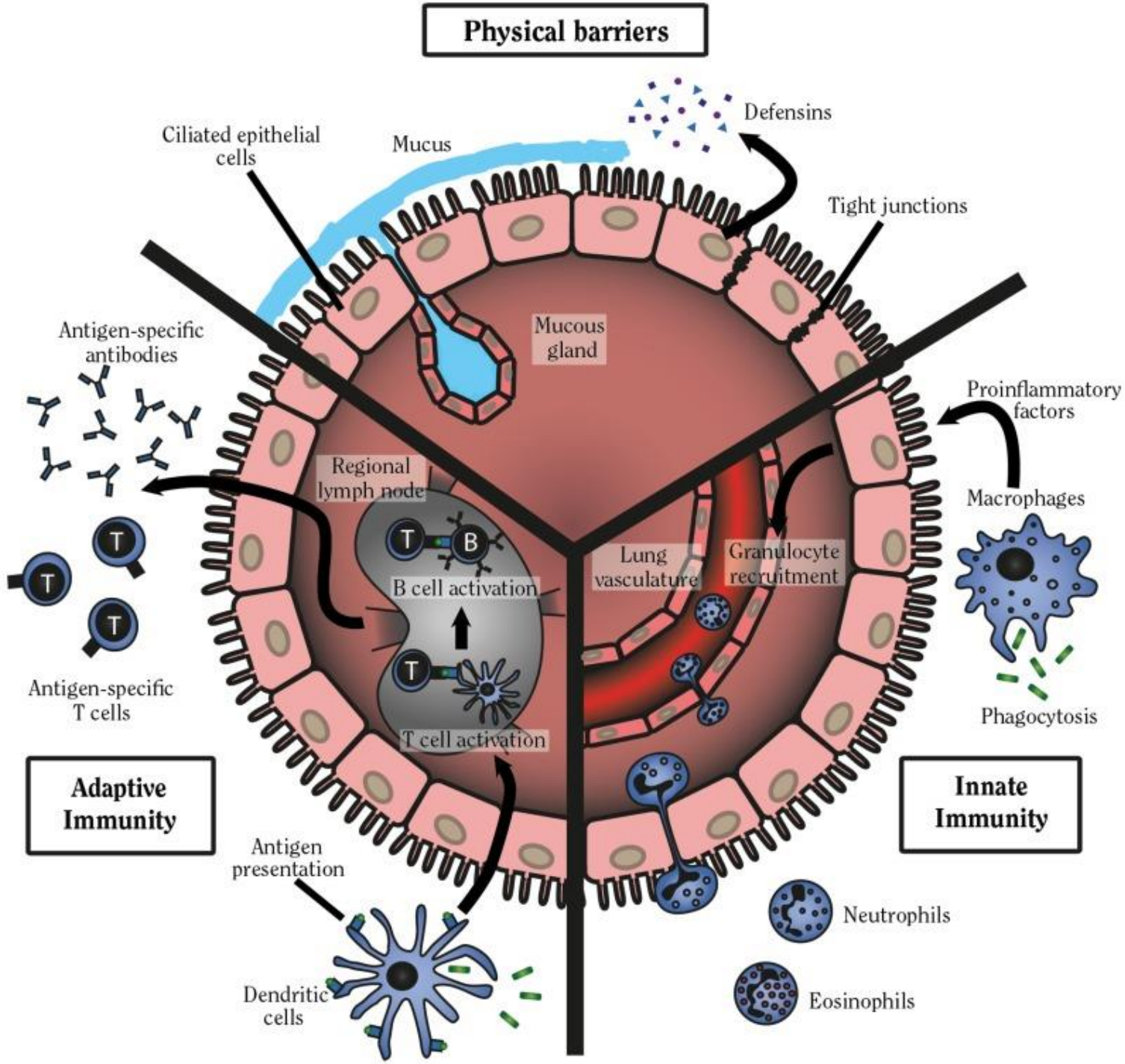


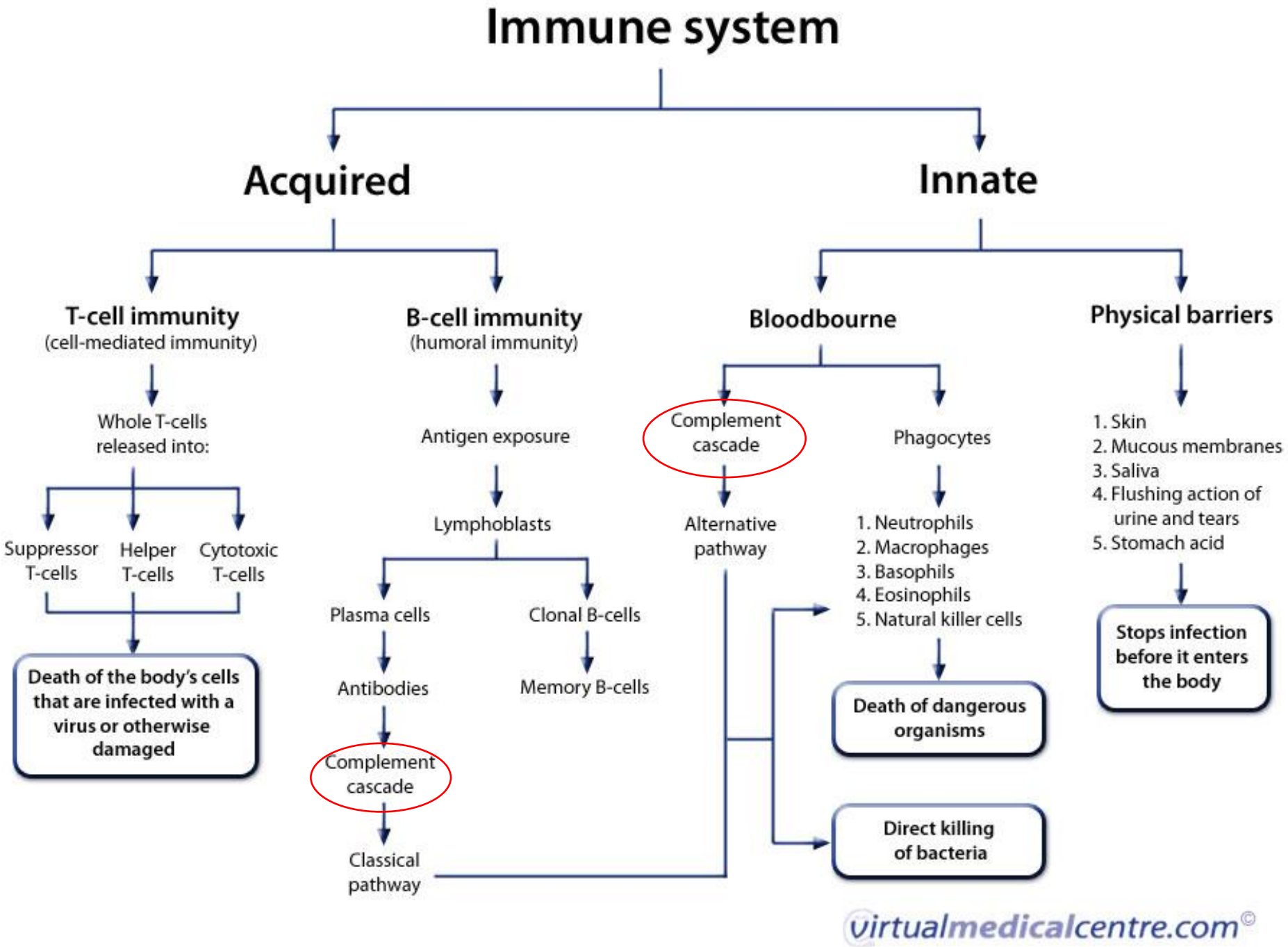
Adaptive Immunity (acquired)
- Cellular (cytotoxic)
- Humoral (antibodies)

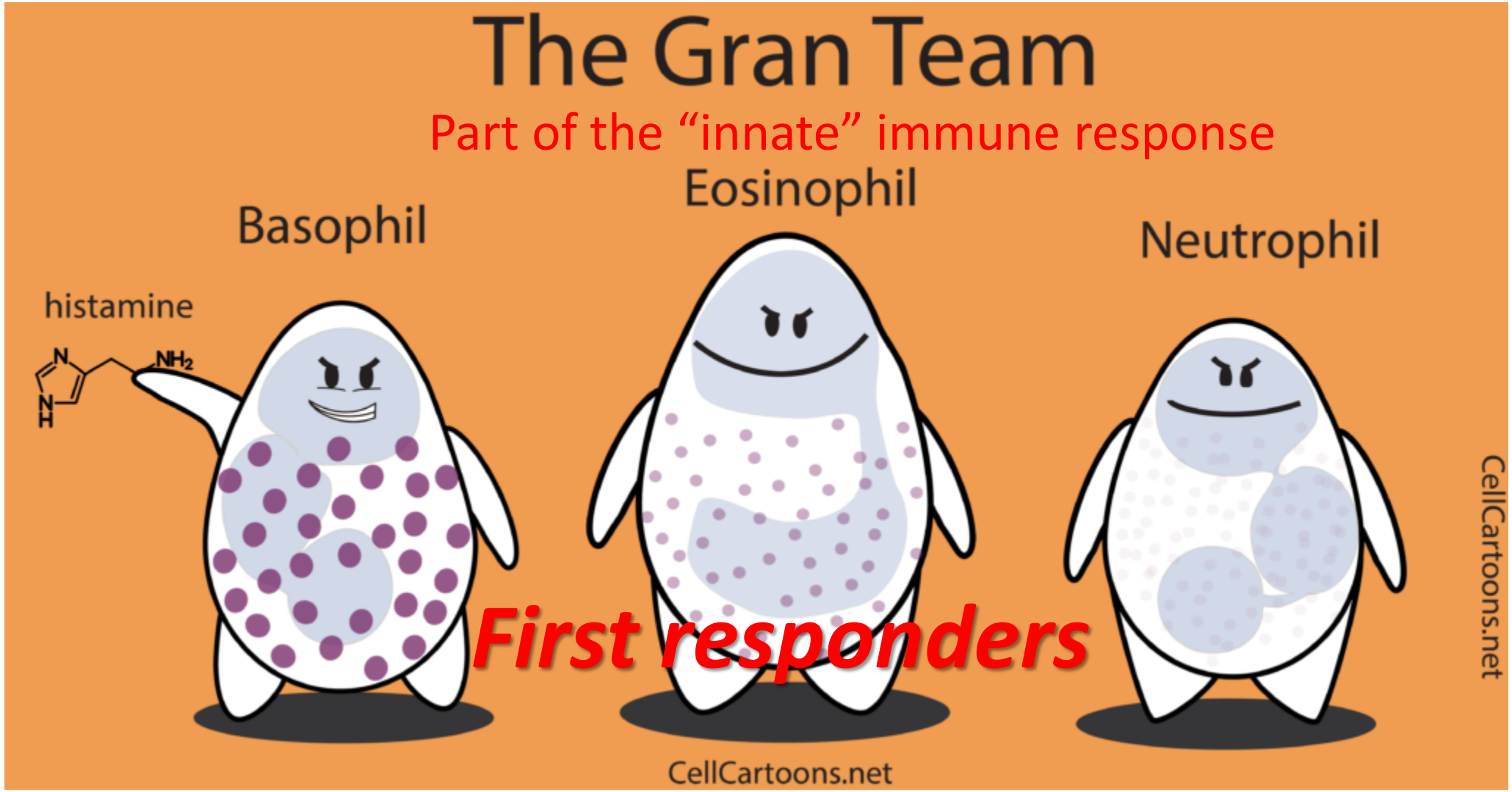
Innate Immunity (natural)
- Macrophages, neutrophils, eosinophils, basophils, monocytes
- The complement system

Non-specific Physical & Chemical Defenses
- Barriers: skin, mucous membranes, stomach acid, lysozyme in tears
- Expulsion: Coughing, sneezing, vomiting, diarrhea

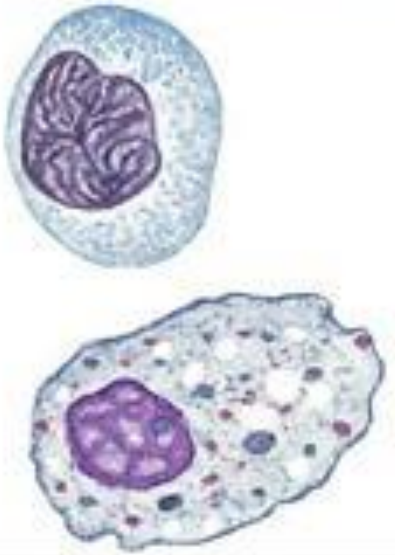
Point of entry for pathogen	Barriers/mechanisms to prevent entry of pathogen
Skin	• Keratinised (scaly) skin cells form an impermeable layer to water & pathogens • Rapid blood clotting & wound healing prevent entry from pathogens
Digestive system	• Lysozymes in saliva, enzymes, & strong acids in stomach break down pathogens
Respiratory system	• Mucus traps dirt & microscopic pathogens, then cilia that line the trachea move the mucus upwards (& out via the mouth)
Reproductive and urinary tract	• Mucus containing acids provides an unfavourable environment to pathogens • Moving fluids/urine flush out pathogens
Sense organs	• Ear wax, nostril hairs and eyelashes trap • Tears wash away pathogens


Physical barriers
Defensins
Ciliated epithelial cells
Mucus
Tight junctions
Antigen-specific antibodies
Mucous gland
Proinflammatory factors
Regional lymph node
Macrophages
T
B
Lung vasculature
Granulocyte recruitment
B cell activation
T
T
T
Antigen-specific T cells
Phagocytosis
T cell activation
Adaptive Immunity
Innate Immunity
Antigen presentation
Neutrophils
Dendritic cells
Eosinophils

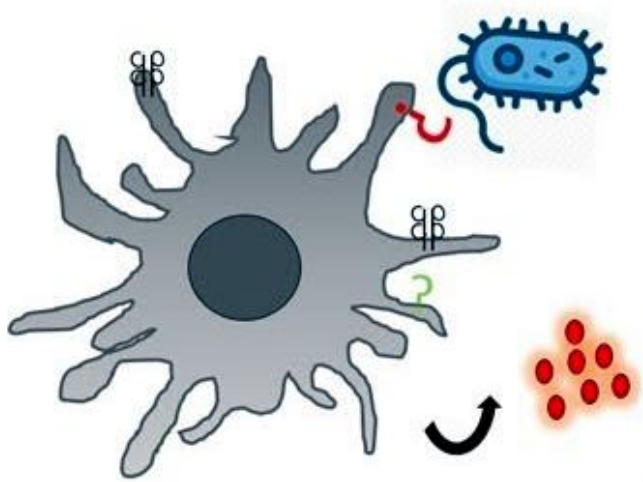


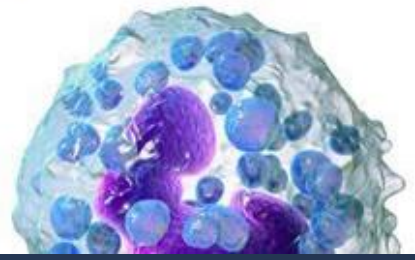

The Gran Team
Part of the “innate” immune response
Eosinophil
Basophil
Neutrophil
histamine
NH2
First responders
CellCartoons.net
CellCartoons.net

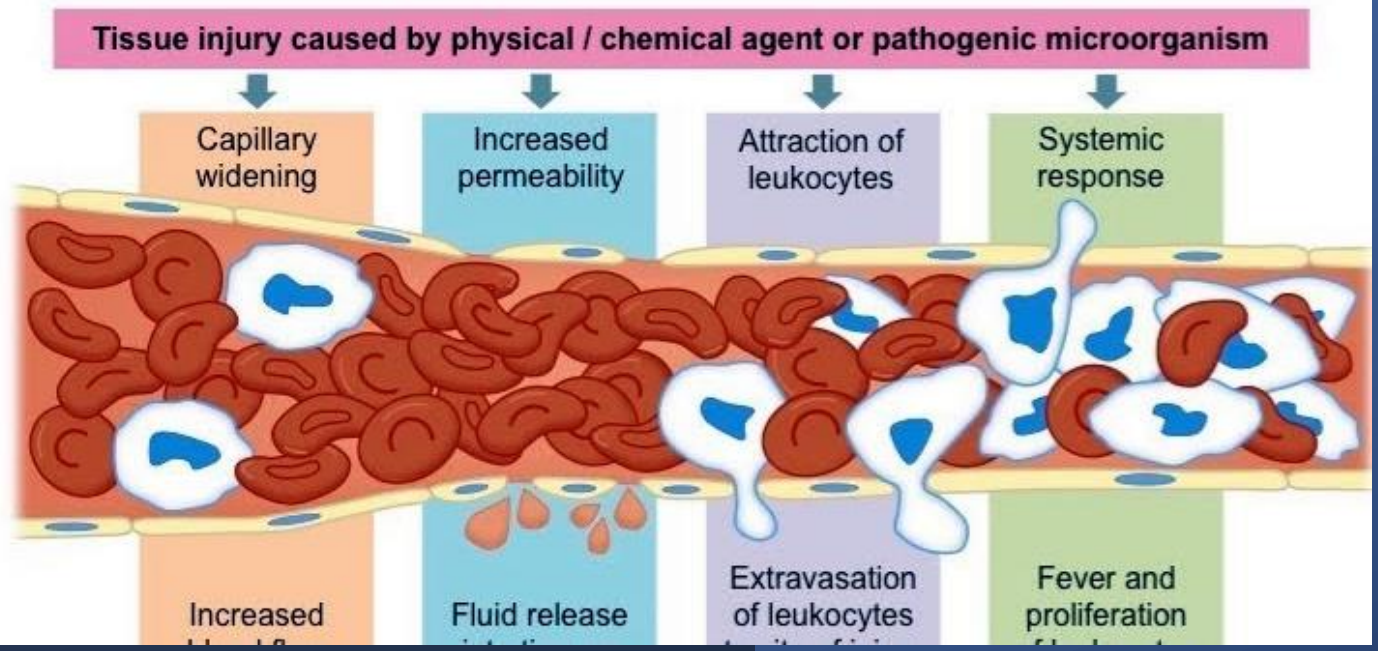
White blood cells (leukocytes) and their function

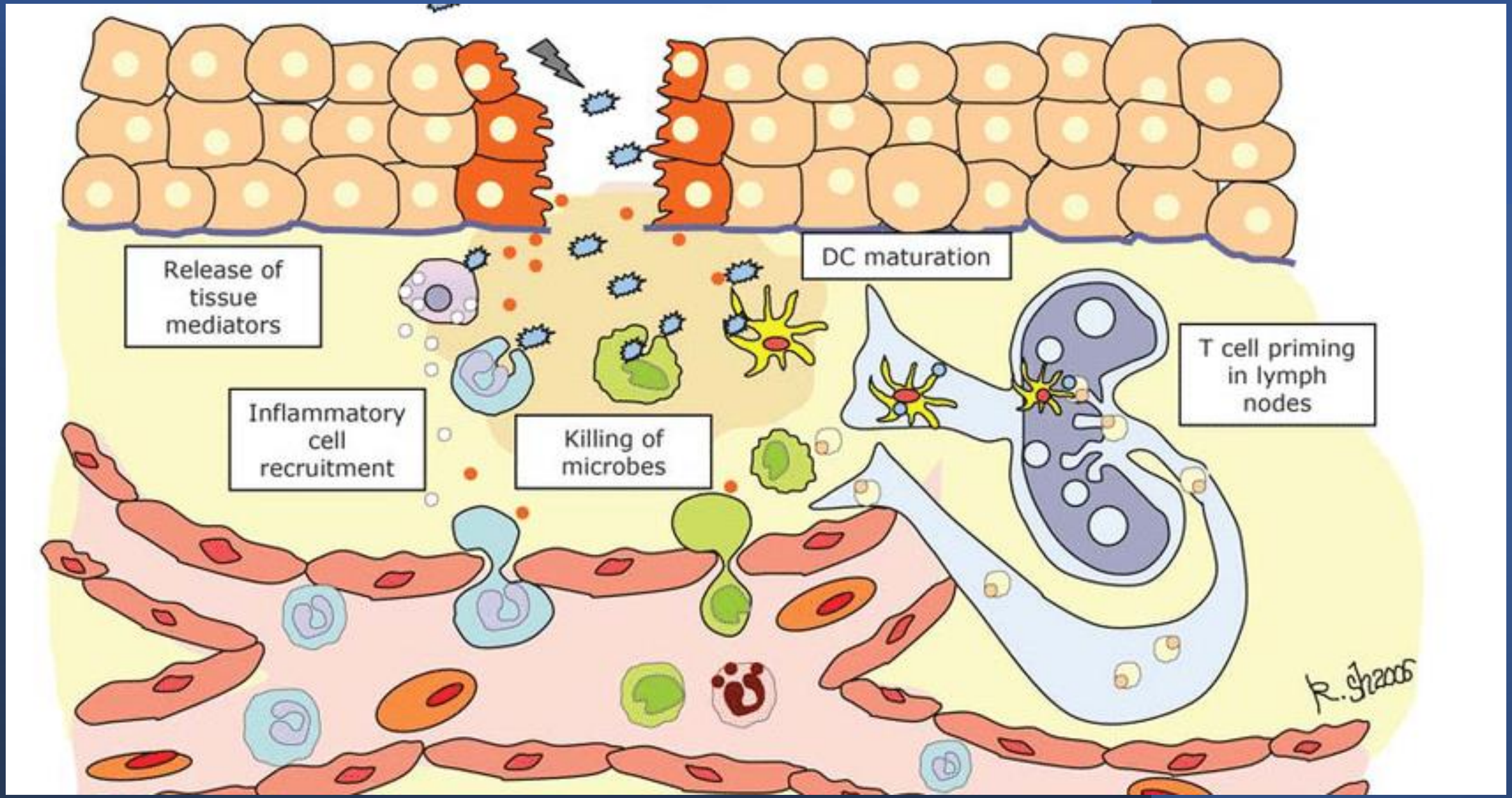
	Basophils and mast cells	*Neutrophils*	*Eosinophils*	*Monocytes and macrophages*	*Lymphocytes and plasma cells*	*Dendritic cells*
						
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation

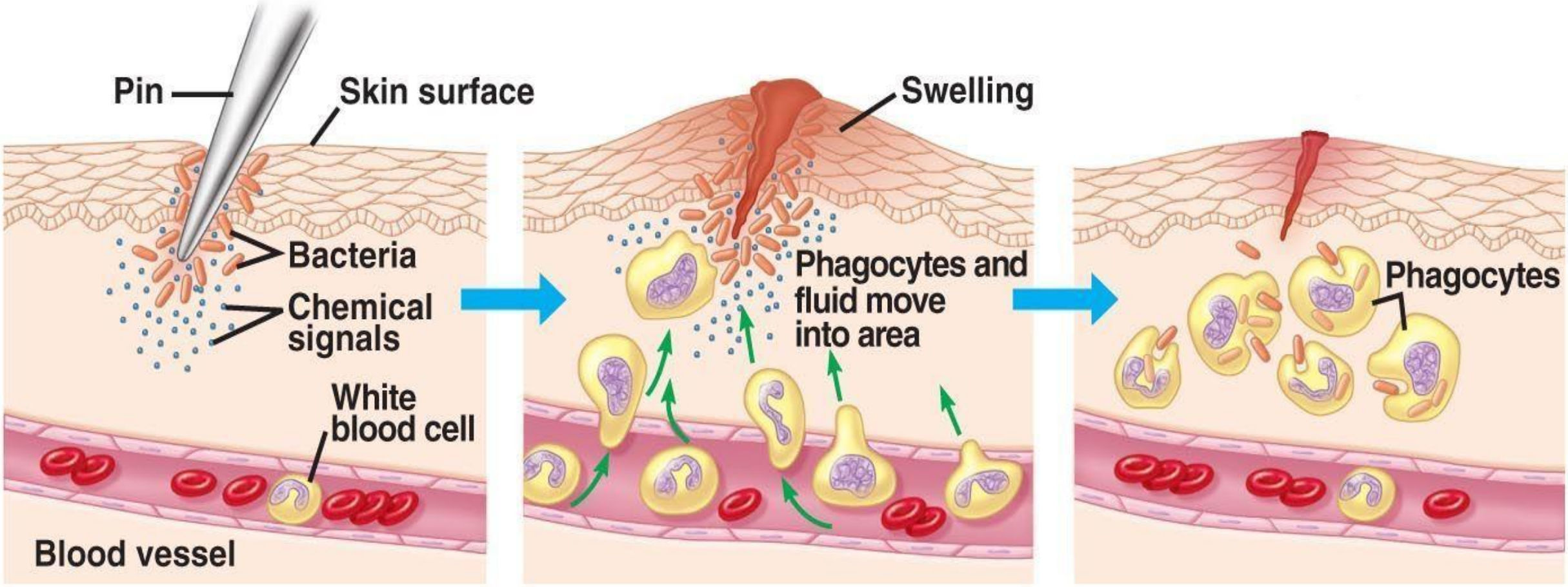
The Inflammatory Response





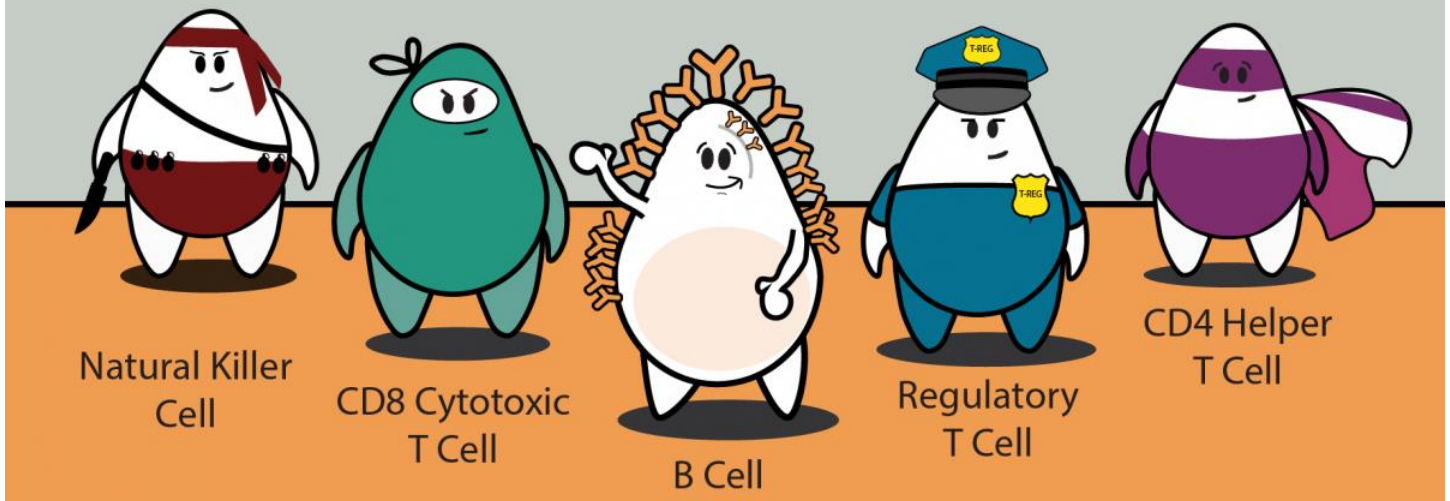



Release of tissue mediators
DC maturation
T cell priming in lymph nodes
Inflammatory cell recruitment
Killing of microbes



1. Tissue injury; release of chemical signals such as histamine
2. Dilation and increased leakiness of local blood vessels; migration of phagocytes to the area
3. Phagocytes (macrophages and neutrophils) consume bacteria and cell debris; tissue heals

Lymphocytes



CellCartoons.net

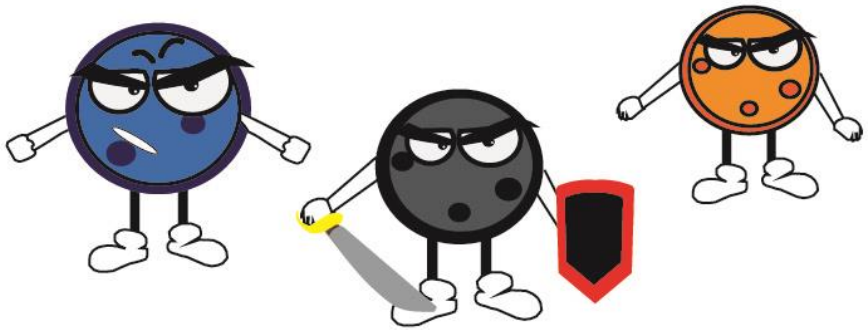
The "Adaptive" Immune system

The Adaptive Immune Response:

Cells that are called in to fight the infection. This response is specific to the type of invader.

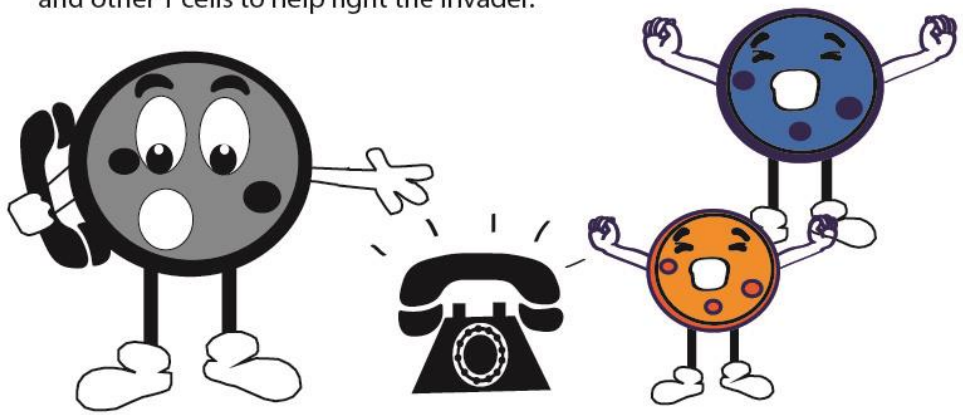
Meet the team:

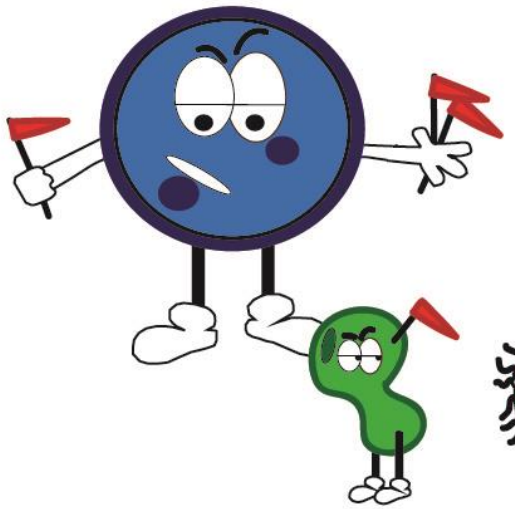
The Special Defense Unit: T cells and B cells



The Helper

Uses chemical signals to call on the B cells and other T cells to help fight the invader.



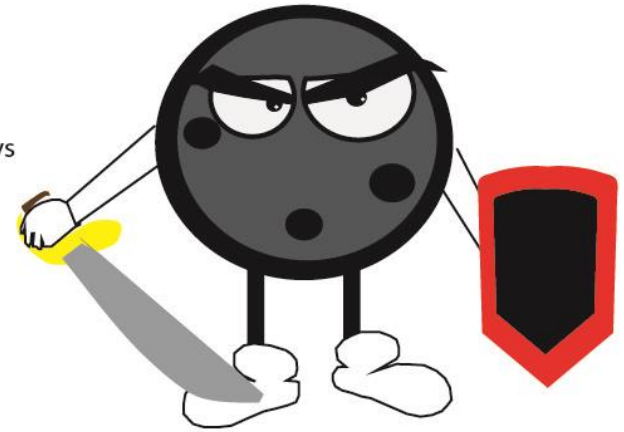


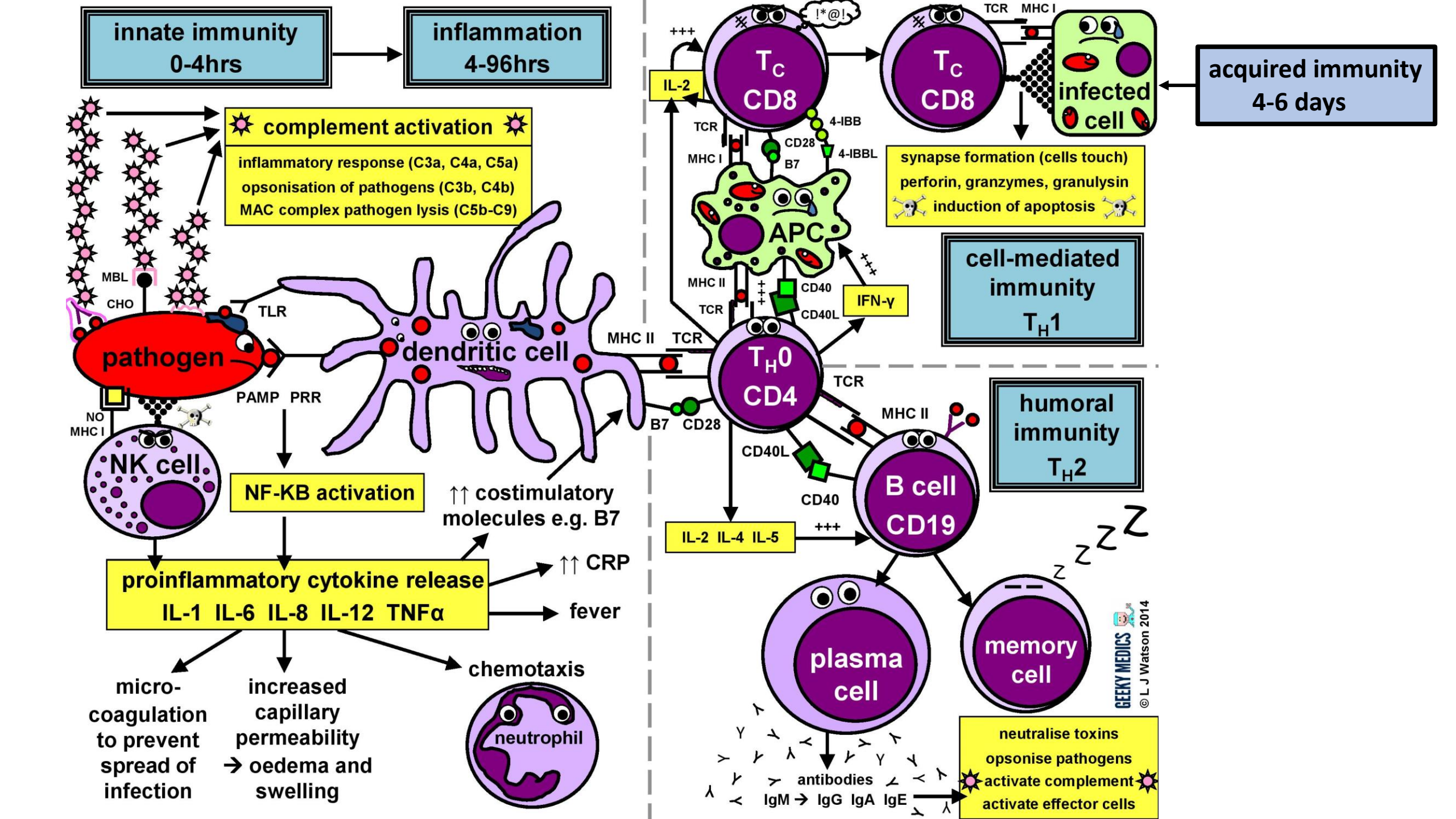
The B Cell

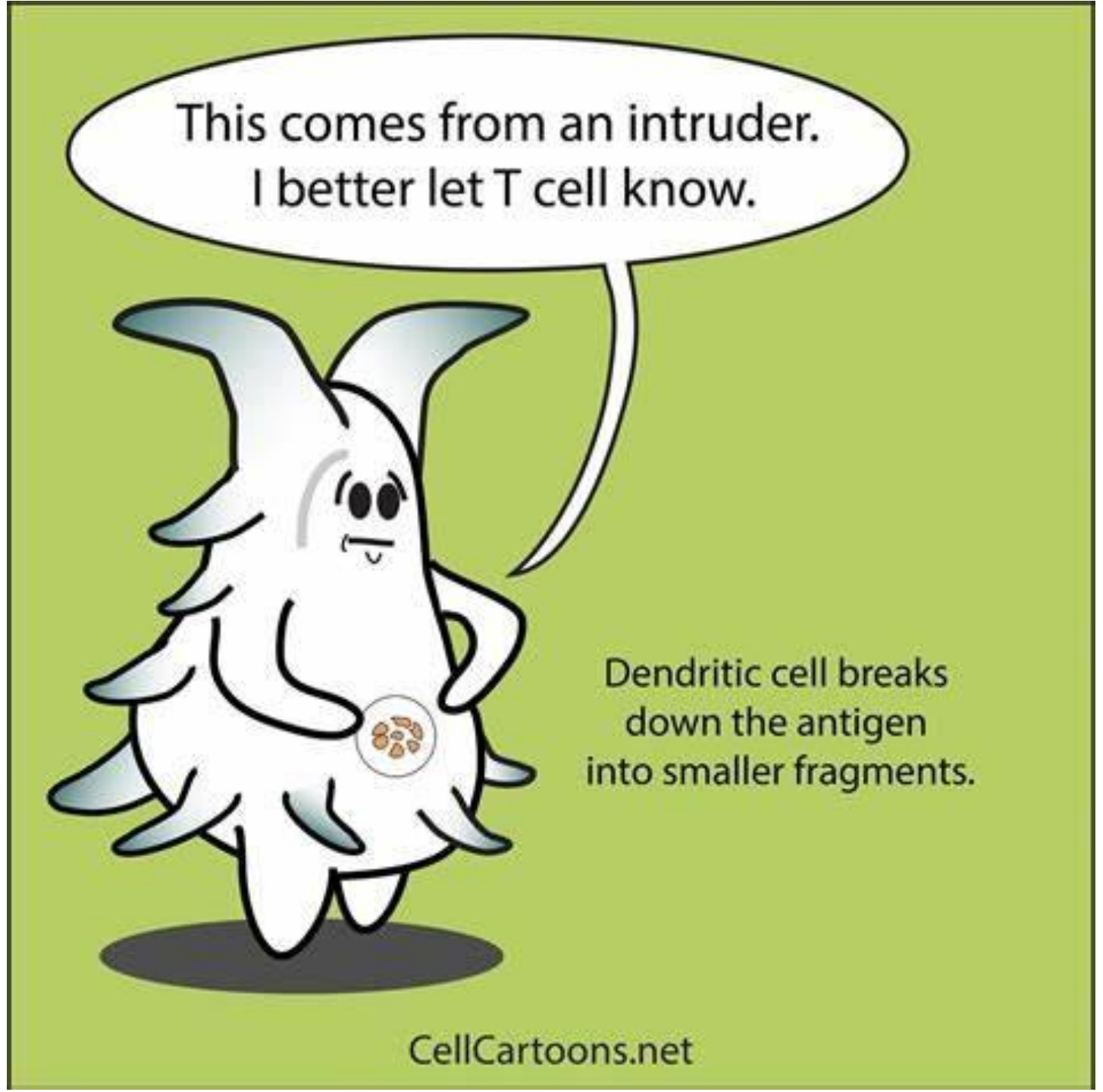
Creates anitbodies that identify foreign invaders that need to be killed.

The Killer

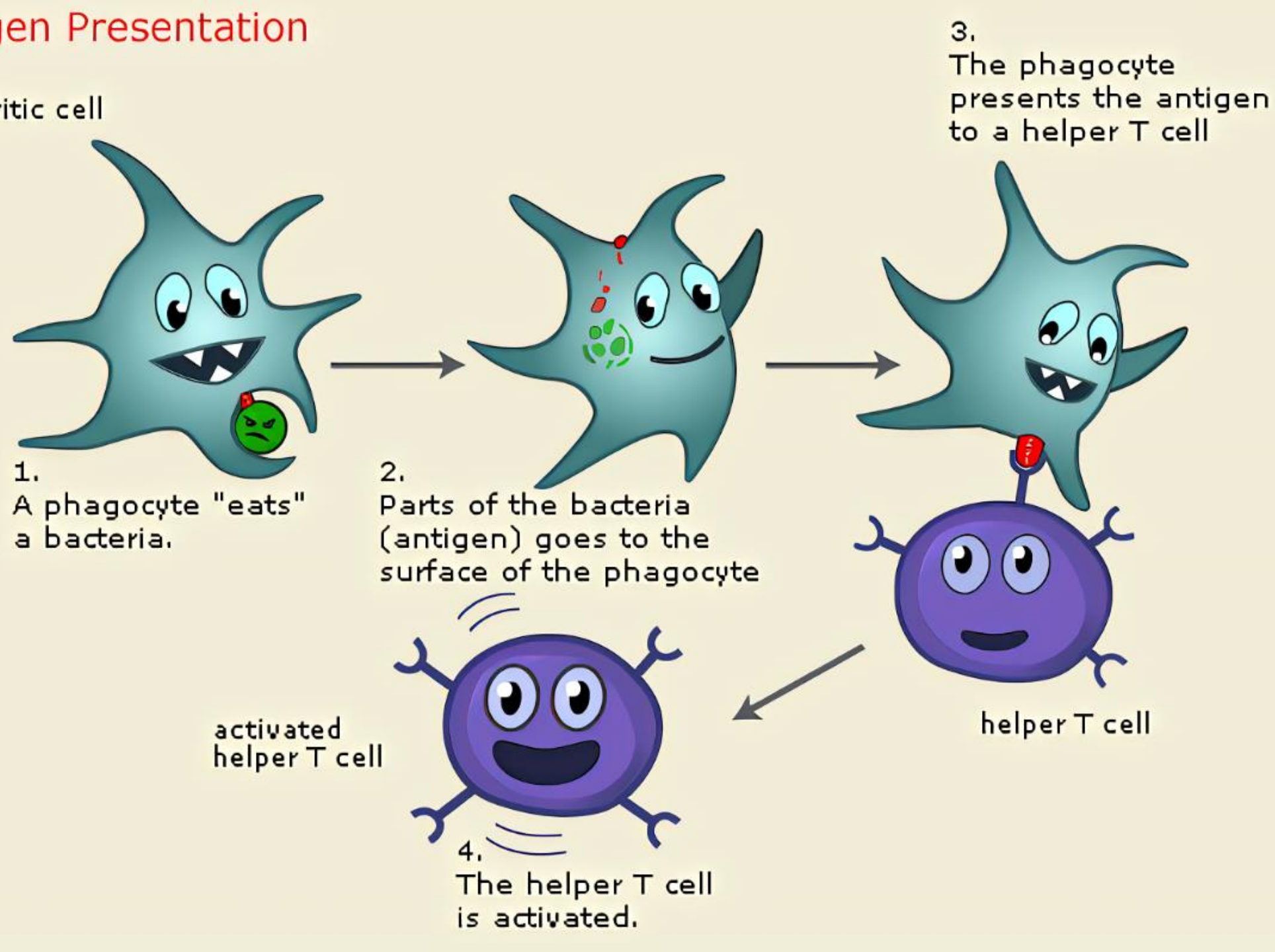
Indentifies infected host cells and employs chemical signals to cause them to die and be eliminated from the body.

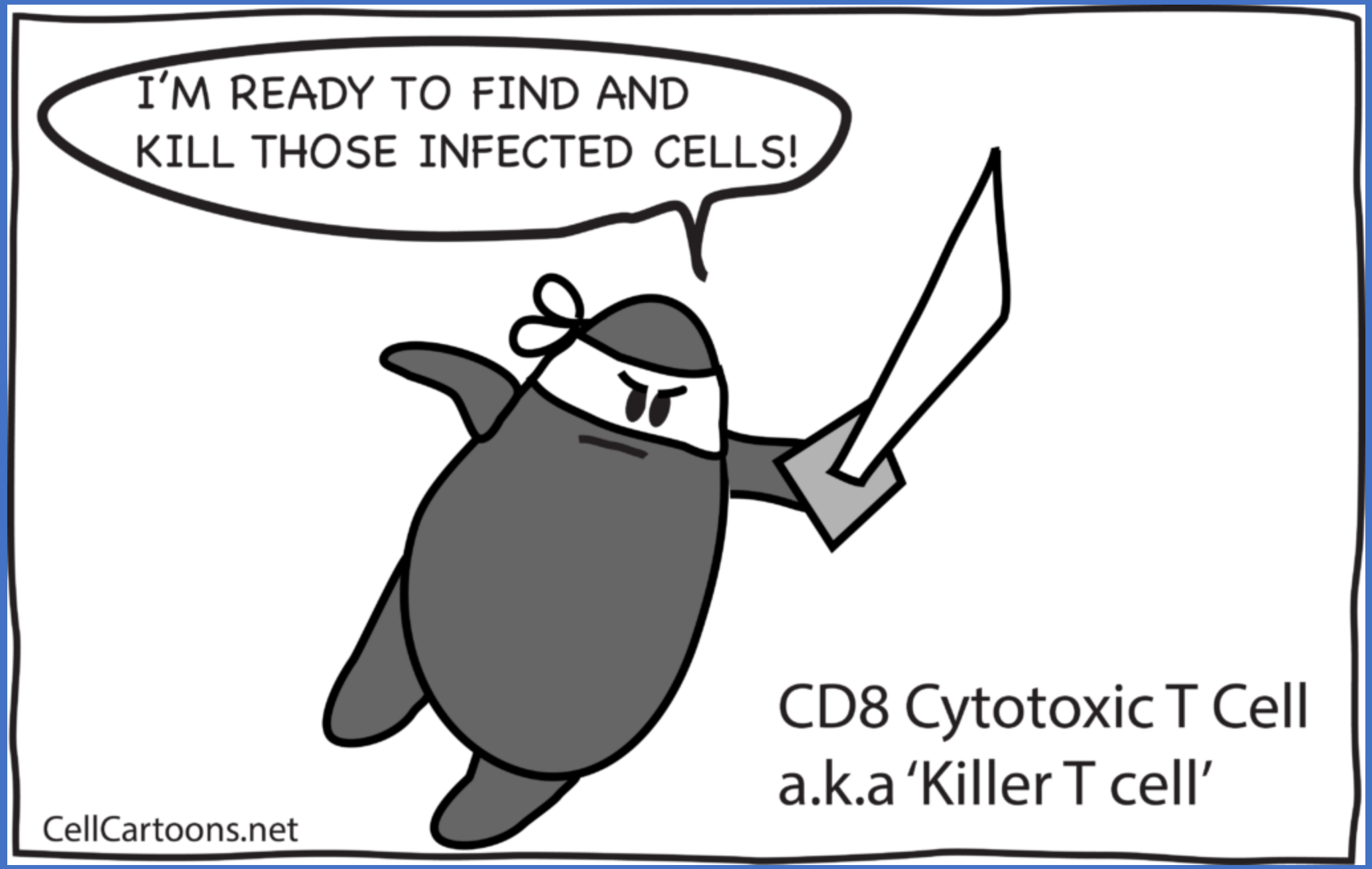



innate immunity
0-4hrs
inflammation
4-96hrs
acquired immunity
4-6 days
complement activation
inflammatory response (C3a, C4a, C5a)
opsonisation of pathogens (C3b, C4b)
MAC complex pathogen lysis (C5b-C9)
MBL
CHO
TLR
pathogen
PAMP
PRR
dendritic cell
NO
MHC I
NK cell
NF-KB activation
↑↑ costimulatory molecules e.g. B7
proinflammatory cytokine release
IL-1 IL-6 IL-8 IL-12 TNFα
↑↑ CRP
fever
chemotaxis
neutrophil
micro-coagulation to prevent spread of infection
increased capillary permeability → oedema and swelling
+++
IL-2
TC CD8
!*@!
TCR
MHC I
4-IBB
CD28
4-IBBL
B7
APC
MHC II
CD40
CD40L
IFN-γ
TH0 CD4
MHC II
TCR
B7
CD28
IL-2 IL-4 IL-5
TC CD8
infected cell
synapse formation (cells touch)
perforin, granzymes, granulysin
induction of apoptosis
cell-mediated immunity
TH1
humoral immunity
TH2
B cell CD19
CD40L
CD40
plasma cell
memory cell
antibodies
IgM → IgG IgA IgE
neutralise toxins
opsonise pathogens
activate complement
activate effector cells
GEEKY MEDICS
© L J Watson 2014

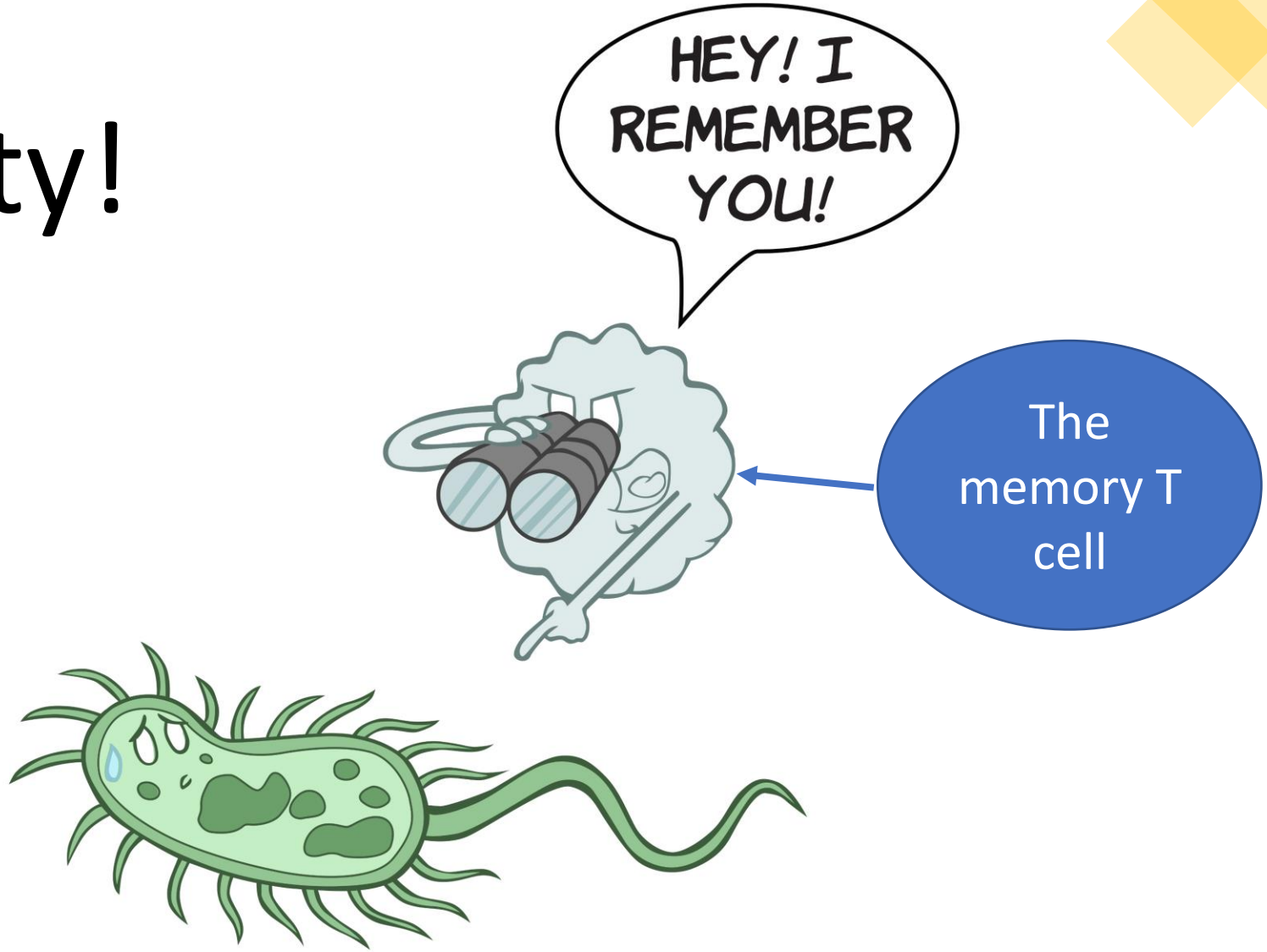

This comes from an intruder.
I better let T cell know.
Dendritic cell breaks
down the antigen
into smaller fragments.
CellCartoons.net

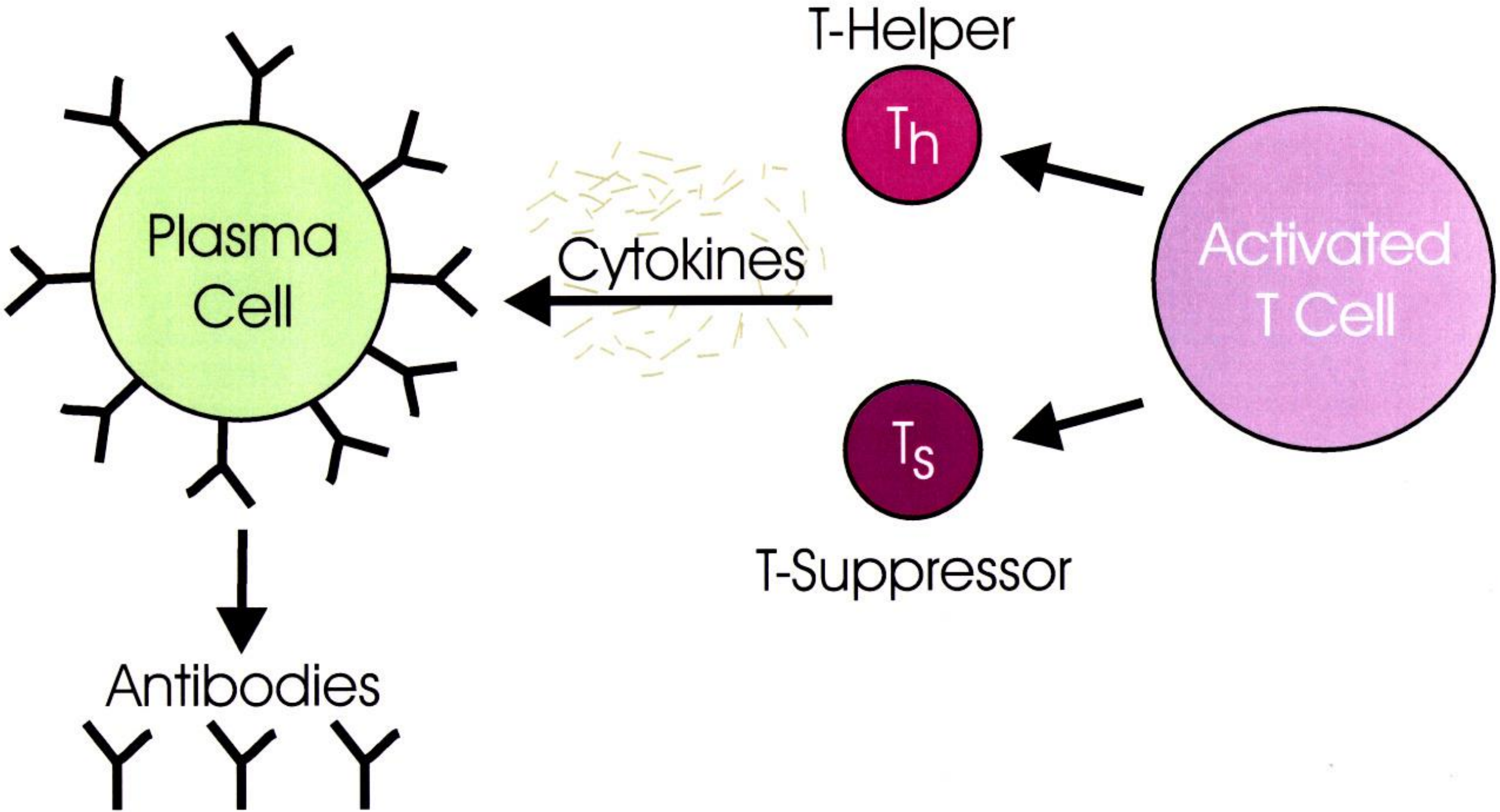
Antigen Presentation

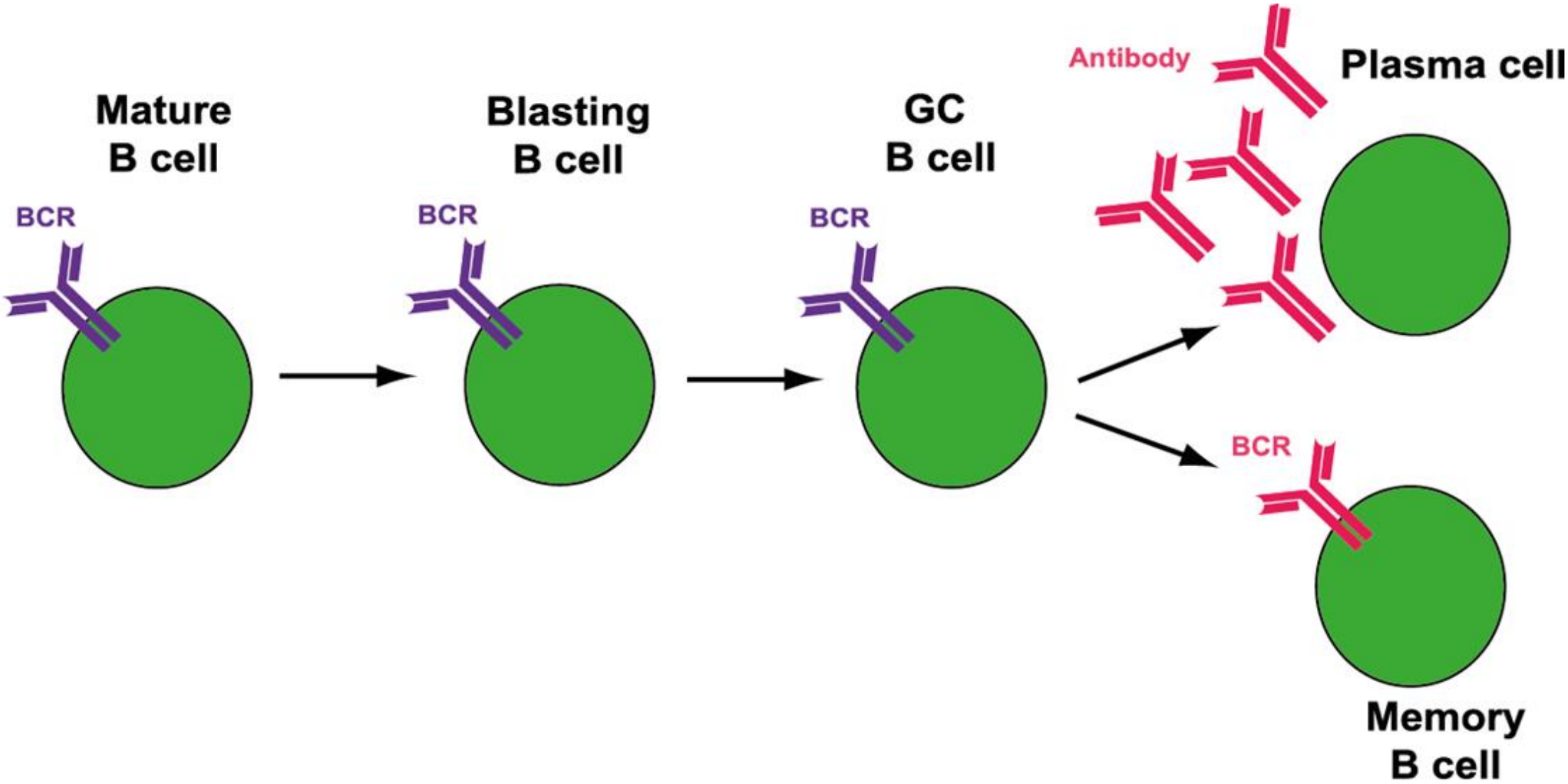


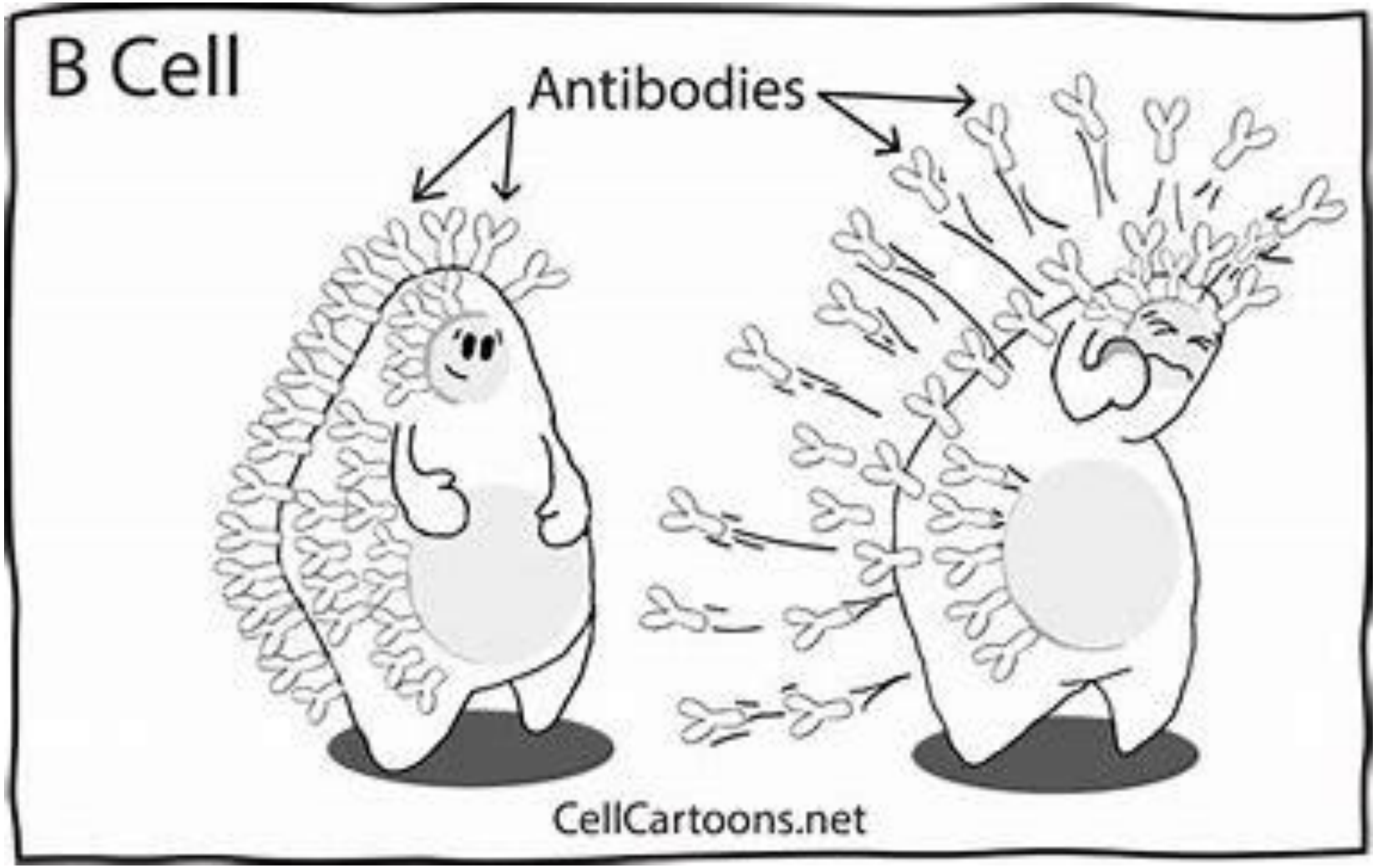

I'M READY TO FIND AND KILL THOSE INFECTED CELLS!
CD8 Cytotoxic T Cell
a.k.a 'Killer T cell'
CellCartoons.net

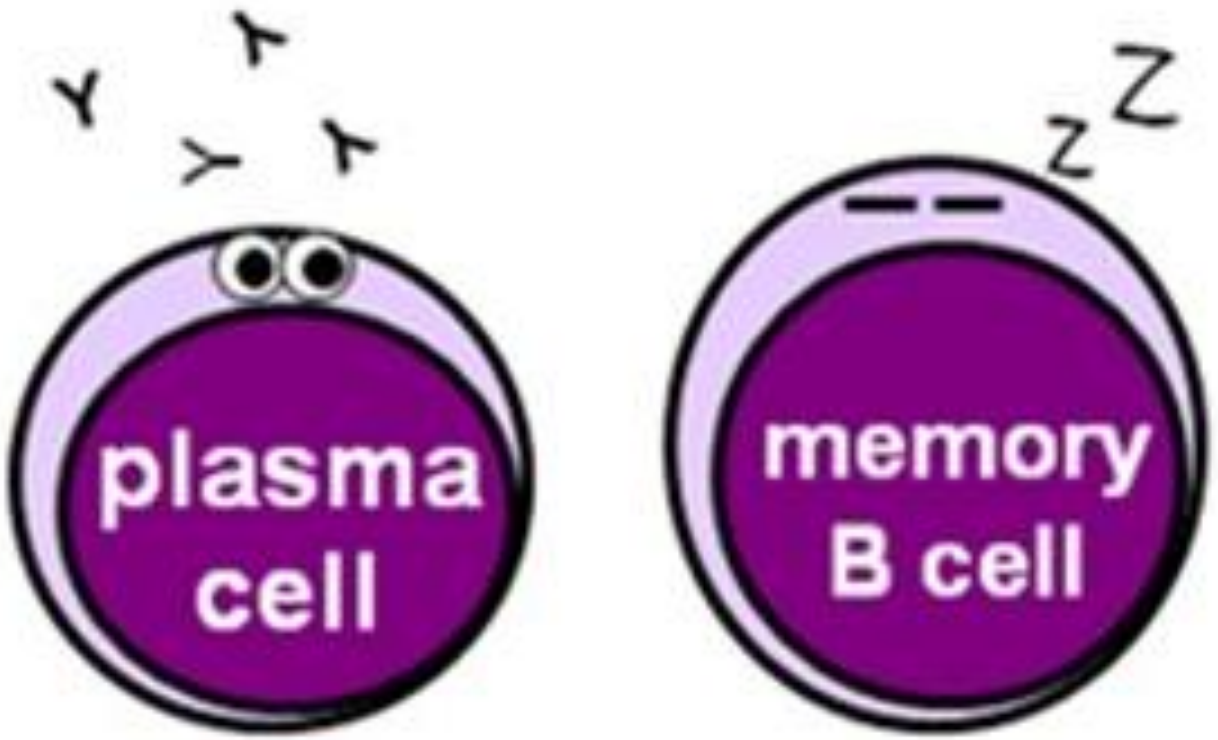
Immunity!



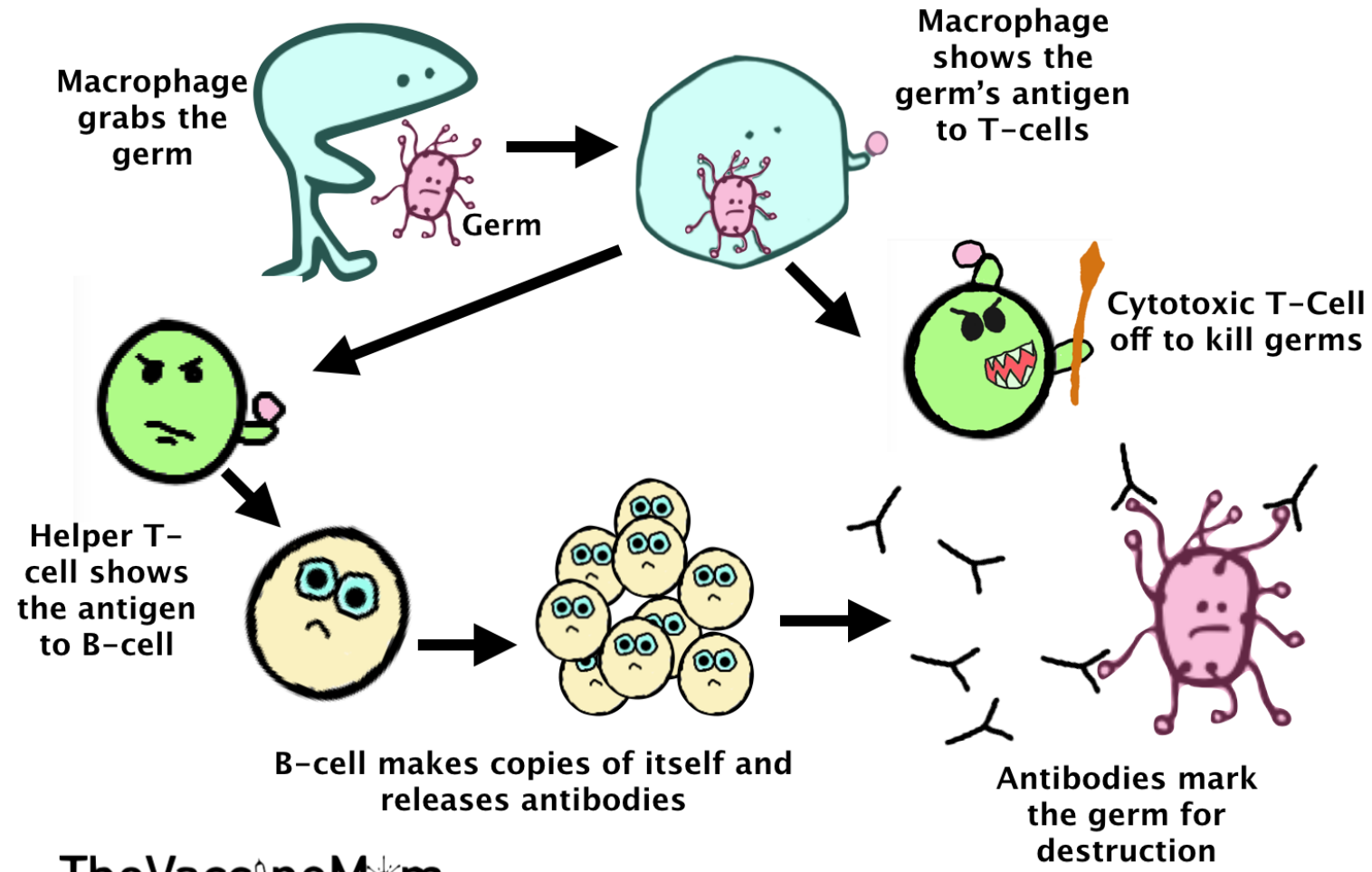

T-Helper
Th
Activated
T Cell
Plasma
Cell
Cytokines
Ts
T-Suppressor
Antibodies


Mature
B cell
BCR
Blasting
B cell
BCR
GC
B cell
BCR
Antibody
Plasma cell
BCR
Memory
B cell


B Cell
Antibodies
CellCartoons.net

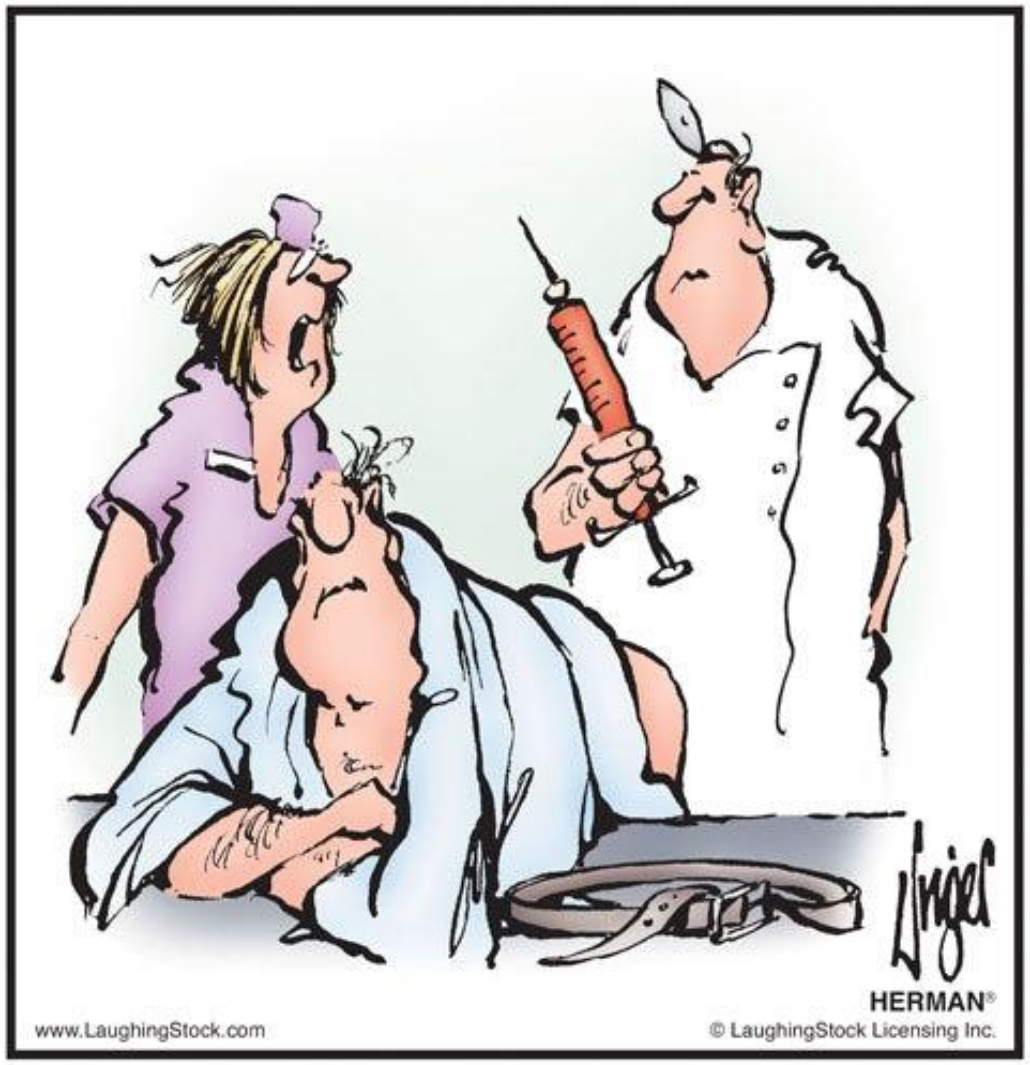

plasma cell
memory B cell

Adaptive Immune System (in a nutshell)

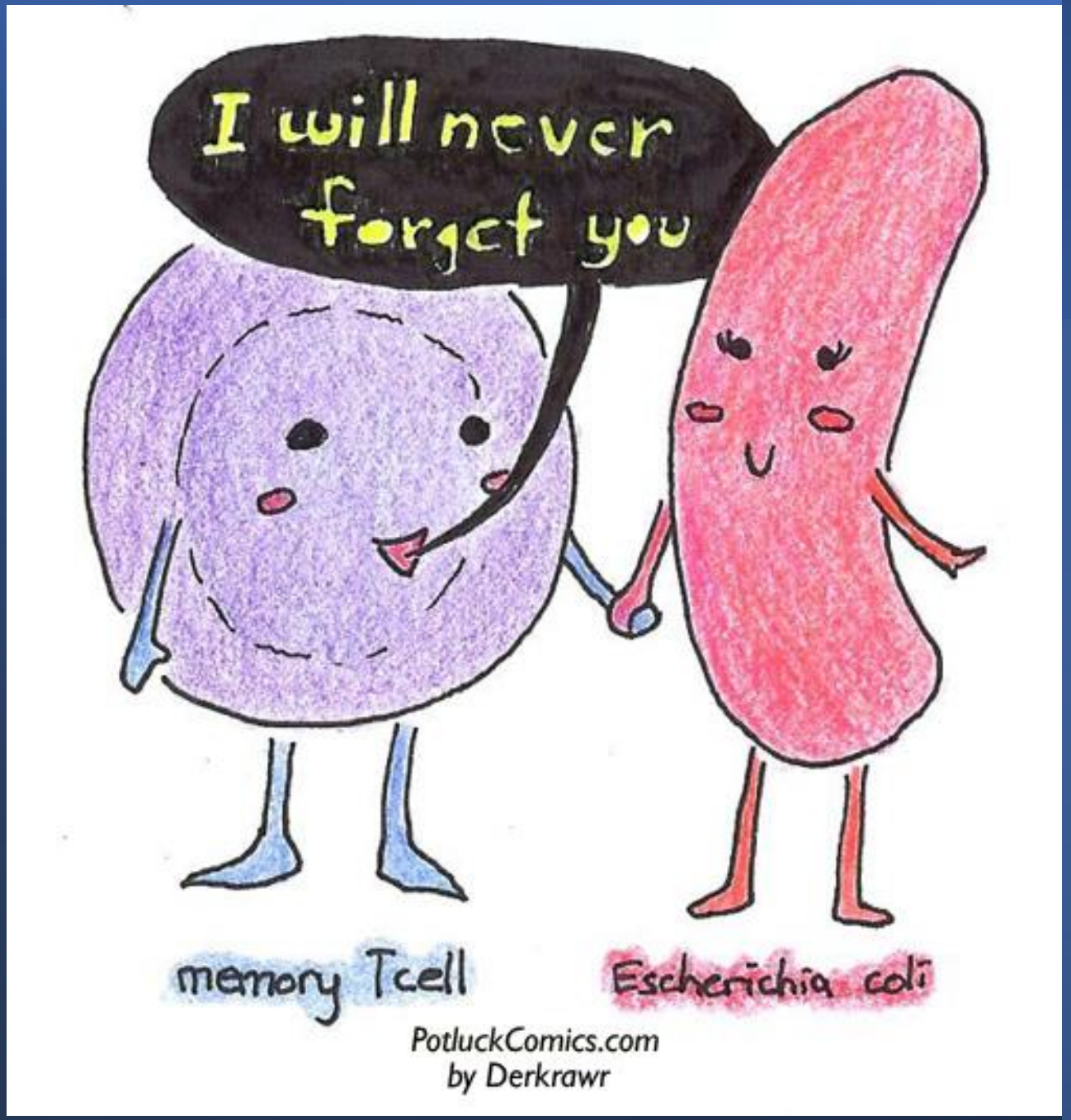


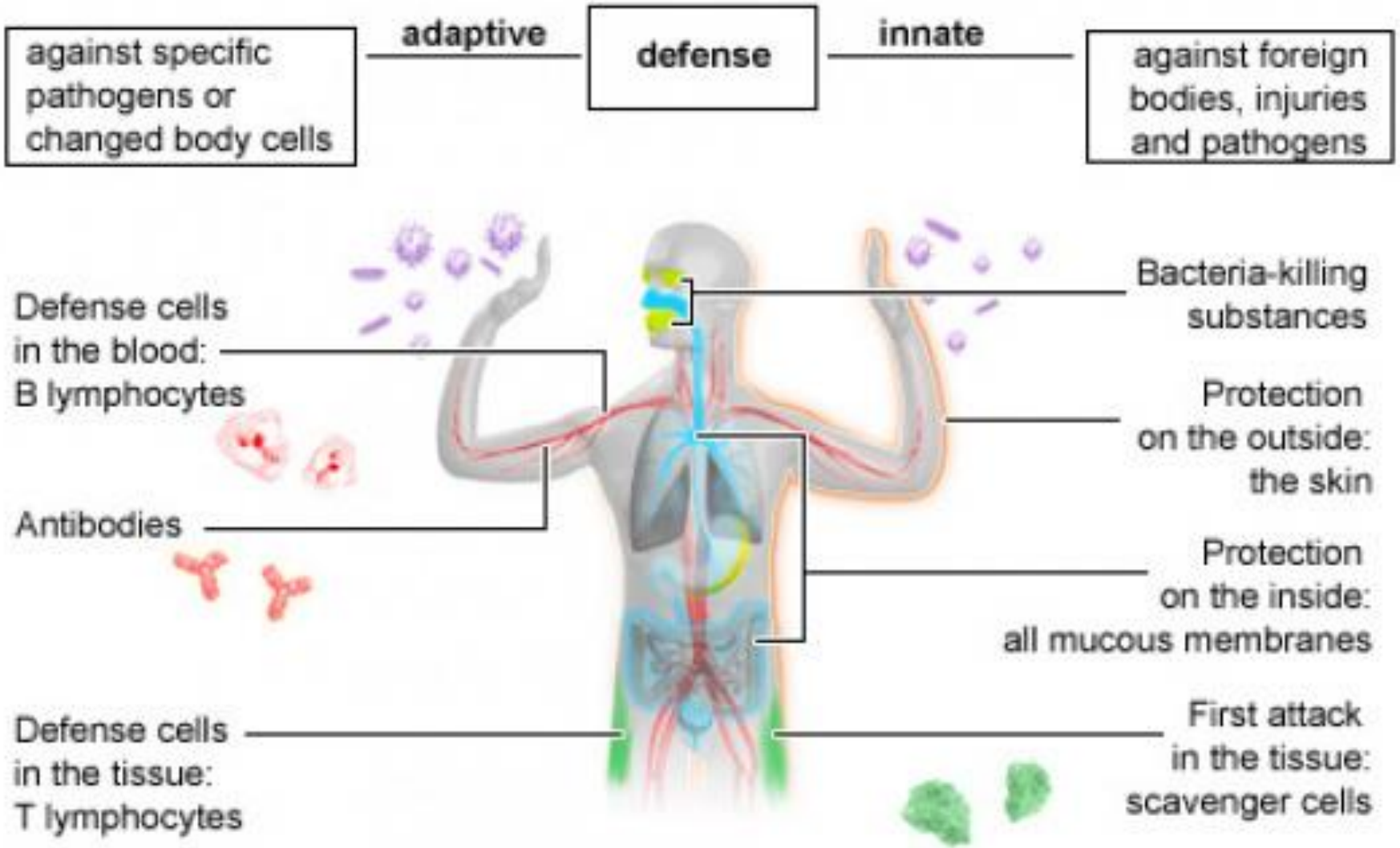
TheVaccineMom

And now for the medical part after this short break



"Oh please! I promise I won't mess it up like last time."


I will never forget you
memory Tcell
Escherichia coli
PotluckComics.com
by Derkrawr


against specific pathogens or changed body cells
adaptive
defense
innate
against foreign bodies, injuries and pathogens
Defense cells in the blood: B lymphocytes
Antibodies
Defense cells in the tissue: T lymphocytes
Bacteria-killing substances
Protection on the outside: the skin
Protection on the inside: all mucous membranes
First attack in the tissue: scavenger cells

Immunization

Dr Chris Pengilly

Immunization

Immunization

- Immunization is most often given by injection into the muscle at the top of the arm (deltoid).
- This ‘not me’ antigen is then discovered by patrolling white cells and the injected vaccine antigen is taken to the local lymph glands in the axilla. They are presented there by the dendritic cells, macrophages and antigen presenting cells.
- The immune system will then create antibodies to destroy the invaders. A number of T lymphocytes will become 'memory cells‘ which will stay dormant until faced with the challenge of this particular antigen

Immunization

- Then the one specific T cell clone, under the direction of the T-helper cell, will increase rapidly to present antibodies and to attack the 'not me‘ antigen.

- Yes – is it not a miracle.

Immunization

There is a variety of types of vaccines – all with the common purpose of preventing illness – working in a variety of ways achieving this common end.

Memory cells will multiply very rapidly in the event of an infection or threat of one.

Immunization

Types of vaccines…

- Inactivated vaccines
- Live-attenuated vaccines
- Sub unit, recombinant, polysaccharide and conjugate vaccines
- Toxoid vaccines
- Viral vector vaccines
- Messenger RNA (mRNA) vaccines

Immunization

Live attenuated vaccines

These use a live but weakened (attenuated) form of the pathogen. The attenuation is usually achieved by serially inoculating the virus, often through chick embryos.

Advantages

Usually affords a long and strong immunity to the pathogen.

Immunization

Limitations

Even though the vaccines are attenuated, they can present serious problems in immunocompromised patients

They need to be kept refrigerated which can limit their use in Third World countries

They can revert very occasionally to a less attenuated form e.g. oral polio

Immunization

Conditions…

- Measles, mumps, rubella, (MMR combined vaccine)
- Rotavirus – *given orally*
- Smallpox (Dr. Edward Jenner in 1796)
- chickenpox and shingles
- yellow fever
- Influenza (nasal spray)
- TB (BCG) bacille Calmette-Guerin intradermal (1908 – 1921)

Immunization

Inactivated vaccines

Here the pathogen is isolated and then (~~killed~~) inactivated by heat, chemicals or radiation.

Advantages

Mostly temperature stable.

Safe and free from complications

Limitations

The immune response is not as robust as a live vaccine

Repeated booster shots may be required.

Immunization

Inactivated vaccines used for…

- Hepatitis A
- influenza
- polio (parenteral only)
- rabies

Immunization

Subunit, recombinant, polysaccharide and conjugate vaccines….

These vaccines are developed by presenting to the host a specific part of the infecting organism. For example a protein or part of the cell membrane. This extract is purified and administered parenterally.

Advantages

Because the vaccine concentrates on a small but distinct area of the infecting organism the response is normally robust.

It is also very safe. It can be given to patients even with severe immunodeficiency.

Limitations

Though the immunization is strong it is not super long-lasting and some will need booster administration occasionally

Immunization

These vaccines can be used to treat…

- Hib (Haemophilus Influenzae Type B)
- Hepatitis B
- HPV (human papillomavirus)
- pertussis (whooping cough)
- pneumococcal disease
- meningococcal disease
- Shingles

Immunization

- These can be combined safely and effectively as *pentavalent vaccine*

- DTaP-IPV/Hib Diphtheria, Tetanus, acellular Pertussis, Polio and Haemophilus influenzae type b

Immunization

Toxoid vaccines

These vaccines do not directly affect the bacteria, but a toxin secreted by the bacteria which causes the symptoms and often death.

Advantages

They are safe and can be administered to immunocompromised patients. They are effective to the point where the target diseases are almost extinct.

They are inexpensive and travel well

Limitations

The immunity is not super long-lasting and usually requires a booster dose every 10 years

Immunization

Conditions treated…

Tetanus and diphtheria.

These vaccines are usually supplied and given together.

Immunization

Viral Vector vaccines

This type of vaccine has been studied for some time, but is still not widely used.
Its mode of action is that a safe part of the infecting organism is attached to a benign virus which carries it into the host. This will be recognized as "not me" and the host's immune system will make and store antibodies.
It is principally used for the “tough cases”.

Advantages

It is a useful research tool and shows great deal of potential.

Conditions treated…

- Zika
- Influenza
- HIV
- SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2)

- Messenger (mRNA) RNA vaccine

- This works by giving the host a small piece of messenger RNA parenterally. This is taken up by the body which responds to the mRNA to make a small piece of the virus spike through which the virus gains access to the host..
- The body senses that this virus fragment comes under the "not me"; the host's immune system will then make antibodies which will be stored by memory T cells.
- If the host should then be attacked by the virus, the combined immune process will recognize the spike protein fragment and the entire virus will be disabled and destroyed.

Advantages

- It Immunizationis relatively quick to manufacture
- it is potentially inexpensive
- the vaccine can readily be "tweaked" as the infecting virus changes
- it has a good safety profile
- Can be given to severely immunocompromised patients

Limitations

- There are rare occasional reports of cardiomyopathy and blood clots
- it has become a victim of widespread militant disinformation which limits its administration to a point where herd immunity not being achieved.
- It is still too expensive for many nations of the Third World

- Conditions treated…

- SARS-CoV-2

Is subject to extensive research which will likely result in a variety of new vaccines – and more excitingly effective cancer treatments.

Immunization

Influenza vaccines available

- Quadrivalent Live Attenuated Influenza Vaccine
- Quadrivalent Inactivated Influenza Vaccines
- High dose quadrivalent Inactivated flu Vaccine

Immunization

Potential Complicatioms

- Egg allergy (Anaphylaxis)
- Guillain-Barré syndrome
- Oculorespiratory syndrome -- characterized by bilateral red eyes or respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, or sore throat) or facial edema occurring within a few hours of influenza immunization and generally resolving within 48 hours.
- A temporary soreness of the arm where the injection was given, a vague malaise for a day or two.

- These complications are unusual and mostly self-limiting

Immunization

The vaccines locally available are all quadrivalent. This means that they are offering protection from four of the most likely flu viruses.

- These are…

- A/Victoria/2570/2019 (H1N1)pdm09-like virus (new strain this year)
- A/Cambodia/e0826360/2020 (H3N2)-like virus (new strain this year)
- B/Washington/02/2019-like virus
- B/Phuket/3073/2013-like virus

Immunization

Quadrivalent Live Attenuated Influenza Vaccine

- This is administered by intranasal spray to each side of the nasal passage.
- It is indicated for individuals from age 2 to 17 years

Immunization

Immunization

Quadrivalent Inactivated Influenza Vaccines

Made from inactivated influenza viruses and is administered as an injection

FLULAVAL® Individuals 6 month of age and older
FLUZONE® Individuals 6 month of age and older
AFLURIA® Individuals 5 years of age and older

Immunization

Quadrivalent Inactivated Influenza Vaccines
High Dose

This vaccine contains four times the antigen load of the regular quadrivalent vaccines.

- Indicated for individuals over 65 years
- living in long term care/assisted living facilities
- living in First Nations communities

Immunization

Adjuvanted influenza vaccine

This is just like the regular quadrivalent inactivated vaccine to which has been added an adjuvant which is found to induce a better immune response in seniors.

MF59 is an oil-in-water emulsion of squalene oil. Squalene, a naturally occurring substance found in humans, animals, and plants, is highly purified for the vaccine manufacturing process.

Immunization

- When do babies start making their own immunity?

Vaccine	2 Months	4 Months	6 Months	12 Months	18 Months	Starting at 4 Years of Age (Kindergarten Entry)
Chickenpox (Varicella) Vaccine (#44b)				✓		
Diphtheria, Tetanus, Pertussis, Hepatitis B, Polio, and *Haemophilus influenzae* type b (DTaP-HB-IPV-Hib) Vaccine (#105)	✓	✓	✓			

Immunization

In the meantime…

Antibodies from the placenta, colostrum and breastmilk

Extra pertussis vaccine during pregnancy

Immunization

What vaccines do I need?

Immunization Schedule for B.C. Adults, Seniors and Individuals at High Risk

Vaccine	Adult	65 Years and Over	High Risk Program†
Chickenpox (Varicella) Vaccine (#44b)[1]	✓		
Hepatitis A Vaccine (#33)			✓
Hepatitis B Vaccine (#25a)[2]	✓		✓
Human Papillomavirus (HPV) Vaccines (101b)[3]	✓		✓
Inactivated Influenza (Flu) Vaccine (#12d)[4]		✓	✓
Measles, Mumps, Rubella (MMR) Vaccine (14a)[5]	✓		
Meningococcal C Conjugate (Men-C) Vaccine (#23a)[6]	✓		
Meningococcal Quadrivalent Vaccine (#23b)			✓
Pneumococcal Conjugate (PCV 13) Vaccine (#62a)			✓
Pneumococcal Polysaccharide Vaccine (#62b)		✓	✓
Tetanus and Diphtheria (Td) Vaccine (#18a)[7]	✓	✓	
Tetanus, Diphtheria, Pertussis (Tdap) Vaccine (#18c)[8]	✓		

Immunization

- Shingles

Immunization

- There are two vaccines available to prevent this dreadful illness.
- Zostavax (Zoster Vaccine Live)
- Shingrix (adjuvanted inactivated)

Autoimmunity

An autoimmune disease is a condition arising from an abnormal immune response to a body part or system.

Previously healthy tissues are attacked by the immune system which misinterprets the “me” tissues as “not me”. It is more than the simple loss or misinterpretation of Major Histocompatibility Complex (MHC).

The sad truth is that in spite of many advances in medicine, the cause, and therefore the cure, for this group of diseases is remaining elusive.

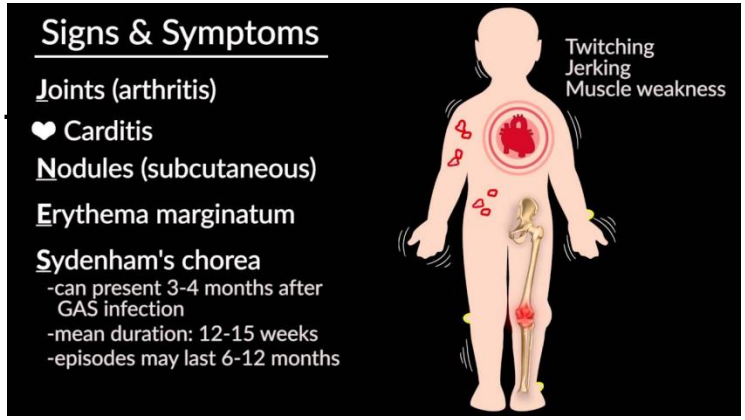
Autoimmunity

Incidence of autoimmune disorders varies from the common to the extremely rare.

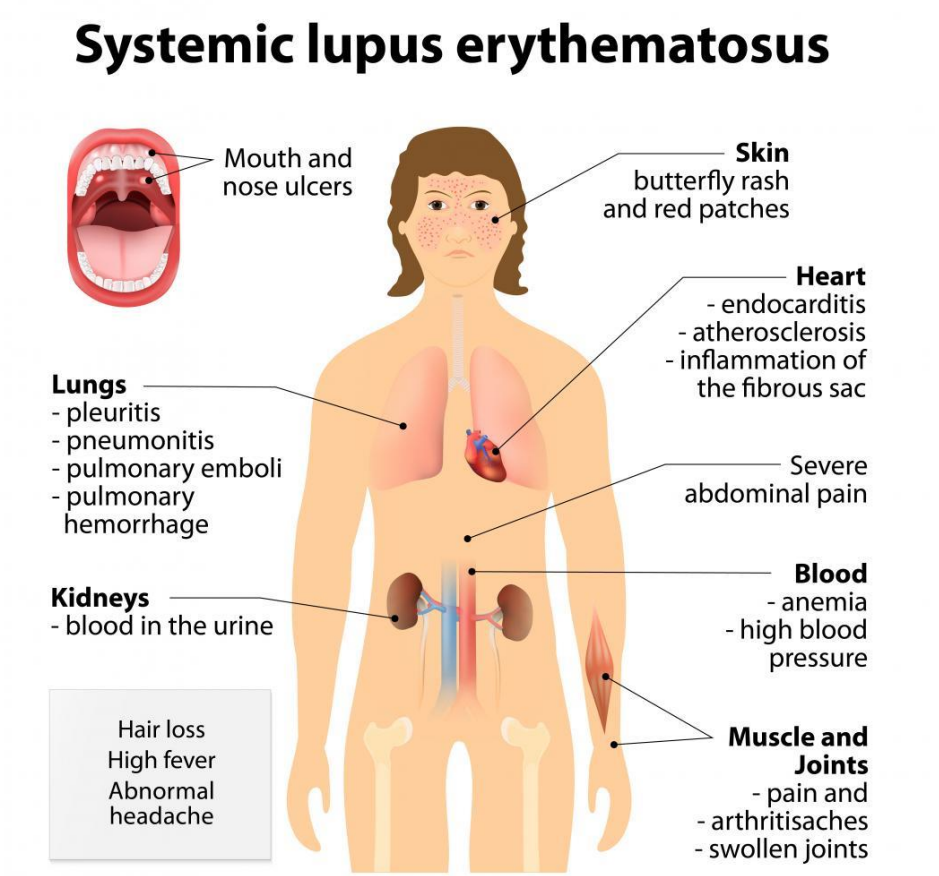
All told there are about 80 different diseases…

Some of the commoner ones are…

- Rheumatoid arthritis.
- Hashimoto's autoimmune thyroiditis.
- Inflammatory bowel disease.
- Graves' disease.
- Diabetes mellitus, type 1
- Vitiligo.
- Rheumatic fever.
- Pernicious anemia/atrophic gastritis
- Psoriasis
- Lupus



Autoimmunity



Autoimmunity

Symptoms can vary considerably. This depends, to a large extent, on which particular tissues are being targeted.

Common to most of these conditions, however, are fatigue, low-grade fever, and general achiness – usually categorized as malaise.

Because of the vague presenting symptoms many of these conditions can be difficult to diagnose.

Autoimmunity

Investigations

Occasionally the diagnosis can be obvious and the investigations focused on that condition – for example the thyroid or rheumatoid arthritis, many, however, present vaguely and need to be investigated.

Such tests include…

C-reactive protein (**CRP**) which is an acute-phase protein of hepatic origin that increases following interleukin 6 secretion by macrophages and T cells; this eventually leads to activation of the complement system.

CRP rises fairly predictably in the presence of inflammation. The test is usually reliable but definitely non-specific.

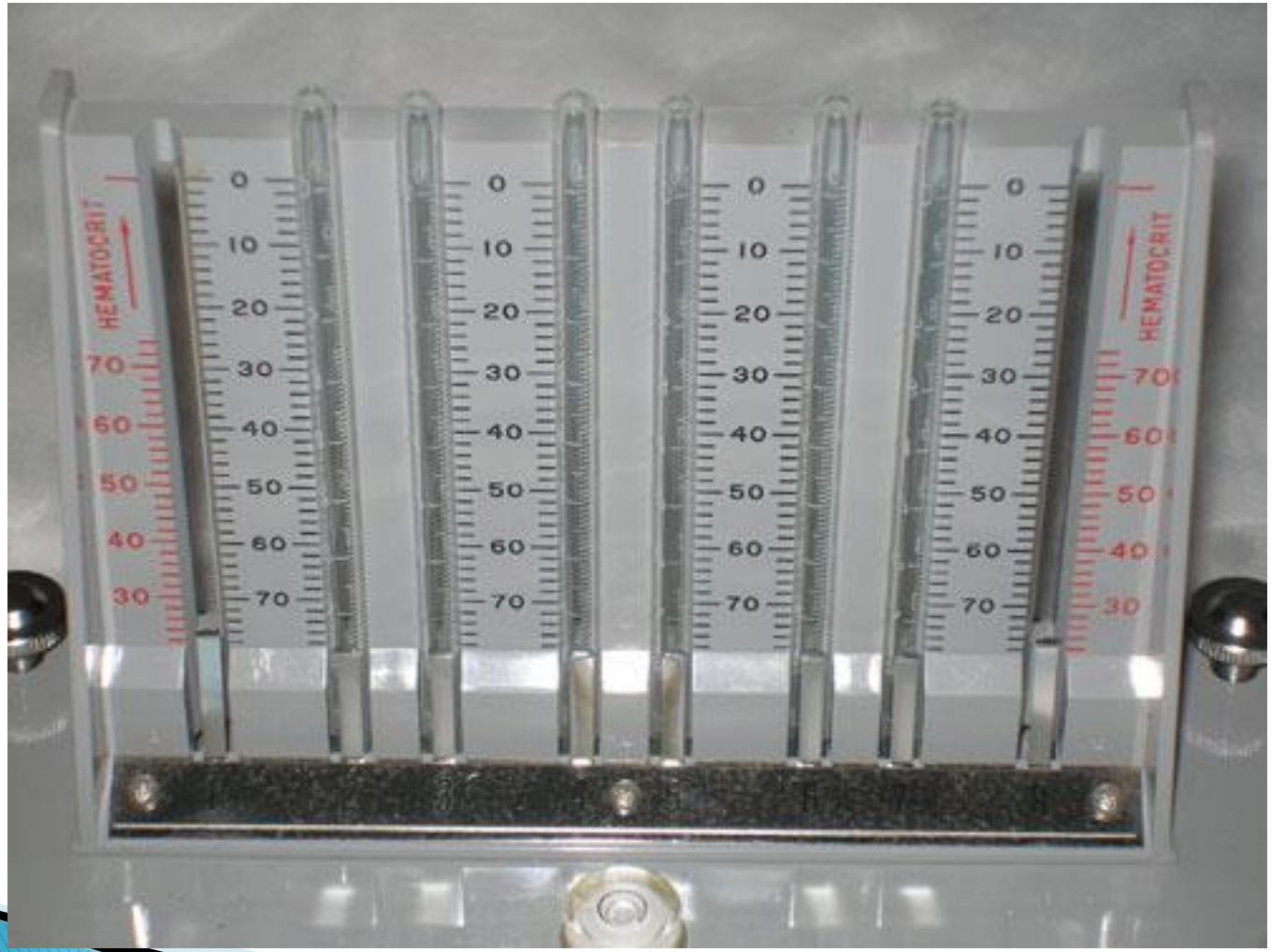
Autoimmunity

Erythrocyte sedimentation rate (ESR) is a much older test, but is a good inexpensive screening tool for inflammation.

Blood is taken from the patient, and anticoagulant is added; it is put in a narrow 200 mm file. After an hour the red blood cells will settle to the bottom of the file. This fall is measured and is the ESR. In healthy individuals a reading of about 4 to 10 mm will be expected and in certain inflammatory conditions it can reach 60 mm.

This test is particularly useful in the diagnosis and treatment of a condition called temporal arteritis.

Immunization



Autoimmunity

Complement blood test measures the amount or activity of complement proteins in the blood. Complement proteins are part of the complement system – that is a group of proteins that work with the immune system to identify and fight disease-causing substances.

A low complement level is strongly indicative of an autoimmune process – classically lupus or rheumatoid arthritis.

Autoimmunity

A much used test used to identify abnormal proteins, is the **antinuclear antibodies**, produced when the body is undergoing an autoimmune attack.

Antinuclear antibodies are autoantibodies — antibodies that target the normal proteins within the nucleus of a cell. This becomes clinically significant when ANAs signal the body to begin targeting itself, which can lead to autoimmune diseases, including lupus, Sjogren's syndrome, and mixed connective tissue disease.

Autoimmunity

Treatment options….

- Symptomatic
- Nonsteroidal anti-inflammatories
- Steroids
- Disease-modifying antirheumatic drugs (DMARDs)
- Several new drugs under investigation

Autoimmunity

Symptomatic treatment…

- Sometimes no treatment is needed at all.
- Safe analgesics for example Tylenol (acetaminophen)
- Lifestyle modifications such as adequate sleep and diet
- Modest alcohol intake
- No smoking
- A regular carefully monitored appropriate exercise program

Autoimmunity

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Can be bought over the counter usually in the form of ibuprofen (Advil) and naproxen

By prescription there are many such as diclofenac (Voltaren)

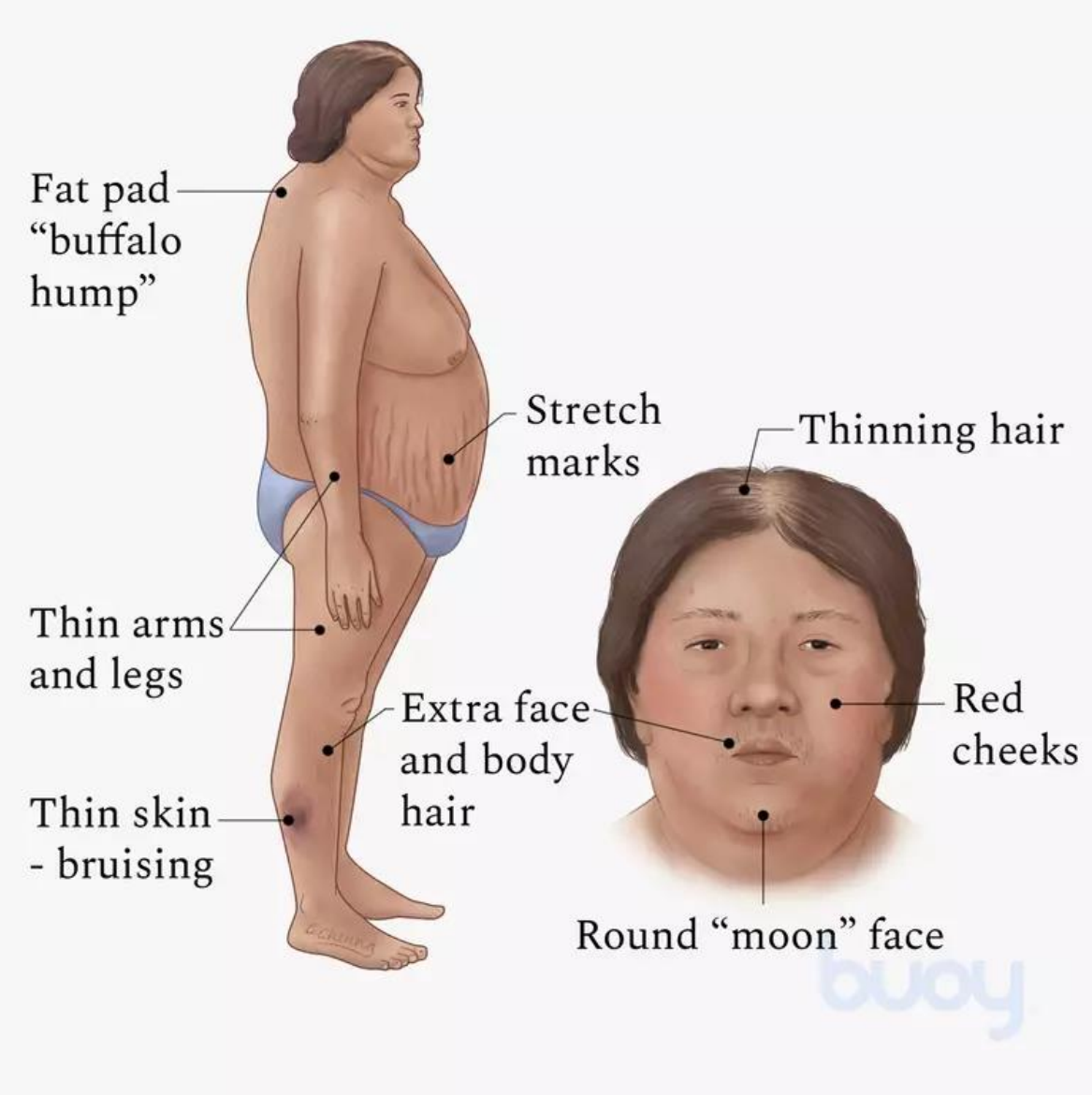
They can all cause significant gastric irritation and occasional bleeding. They are often given with a medication to reduce stomach acid. Another secret is to take them while standing up with a big glass of water and without food.

Autoimmunity

Steroid medications…

- This group medications are potently anti-inflammatory, but do come with significant adverse side effects.
- Cortisone is a human hormone. This has become increasingly used, and provides very useful tools "to put out the fires" – that is to say to treat the more severe symptoms which quite often present at the initial weeks or months of the illness.
- This group of medications include hydrocortisone, prednisone, prednisolone, dexamethasone in order of potency
- In the short term they are mostly harmless, but prolonged exposure or high exposure lead to weight gain, osteoporosis, impaired glucose tolerance, muscle wasting and very occasionally psychosis.

Autoimmunity



Autoimmunity

- Disease-modifying antirheumatic drugs (DMARDs)
- Commonly used conventional DMARDs include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine.
- Generally these medications are well-tolerated. They are usually started at a low dose and gradually increased to the minimum effective dose. There is a long latent period before they become effective – usually around 6 to 8 weeks and possibly longer.
- The aim of these drugs is to reduce the amount of pain but even more so to reduce or slow down joint damage and subsequent debility

Immunisation

Autoimmunity

Biologic disease-modifying antirheumatic drugs (DMARDs), also known as "targeted biologic agents," "biologic agents," or simply "biologics," are DMARDs that are produced using molecular biology (recombinant DNA) techniques.

Some examples are…

- Tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab
- Biologics that target other molecules, including abatacept, rituximab, tocilizumab, sarilumab, and anakinra
- All of these agents are given by injection or infusion, and are under the province of not just specialist, but super specialists..