A New Look for Monoclonal Antibodies (mAbs)

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Disclosures

- Nancy Munro RN, MN, CCRN, ACNP, FAANP has no financial relationships with commercial interests to disclose
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

NIH =

Nerd In Heaven

Objectives

At the end of this presentation, the participant will be able to:

- Explore the role of monoclonal antibodies in immunomodulation
- Identify the scientific rationale(s) for selecting a 'drug of choice' selection, including evidence-based guidelines
- Analyze the mechanism of action and the side effects of mAb and their associated treatments

Monoclonal Antibodies (mAbs)

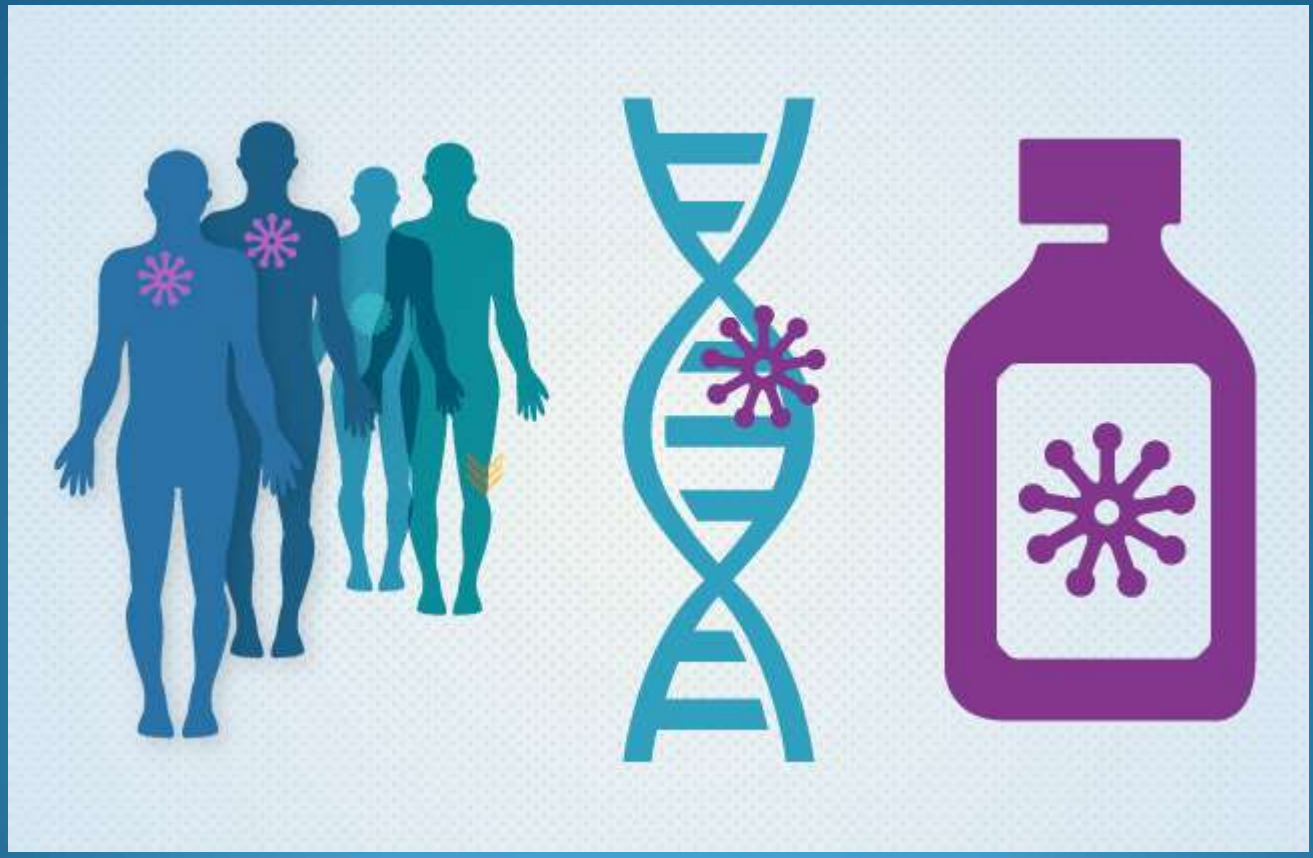
"Targeted Therapy"

Immunity Concepts

Immunomodulation

The adjustment of the immune system response using substances that activate or depress its function

Targeted Therapy



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Immunity Concepts

- Response where the body recognizes a foreign substance and develops a specific response against the substance
- Involves antigens and antibodies
  * ***Antigen*** is a foreign substance
  * ***Antibodies*** is protein produced as a result of a specific response

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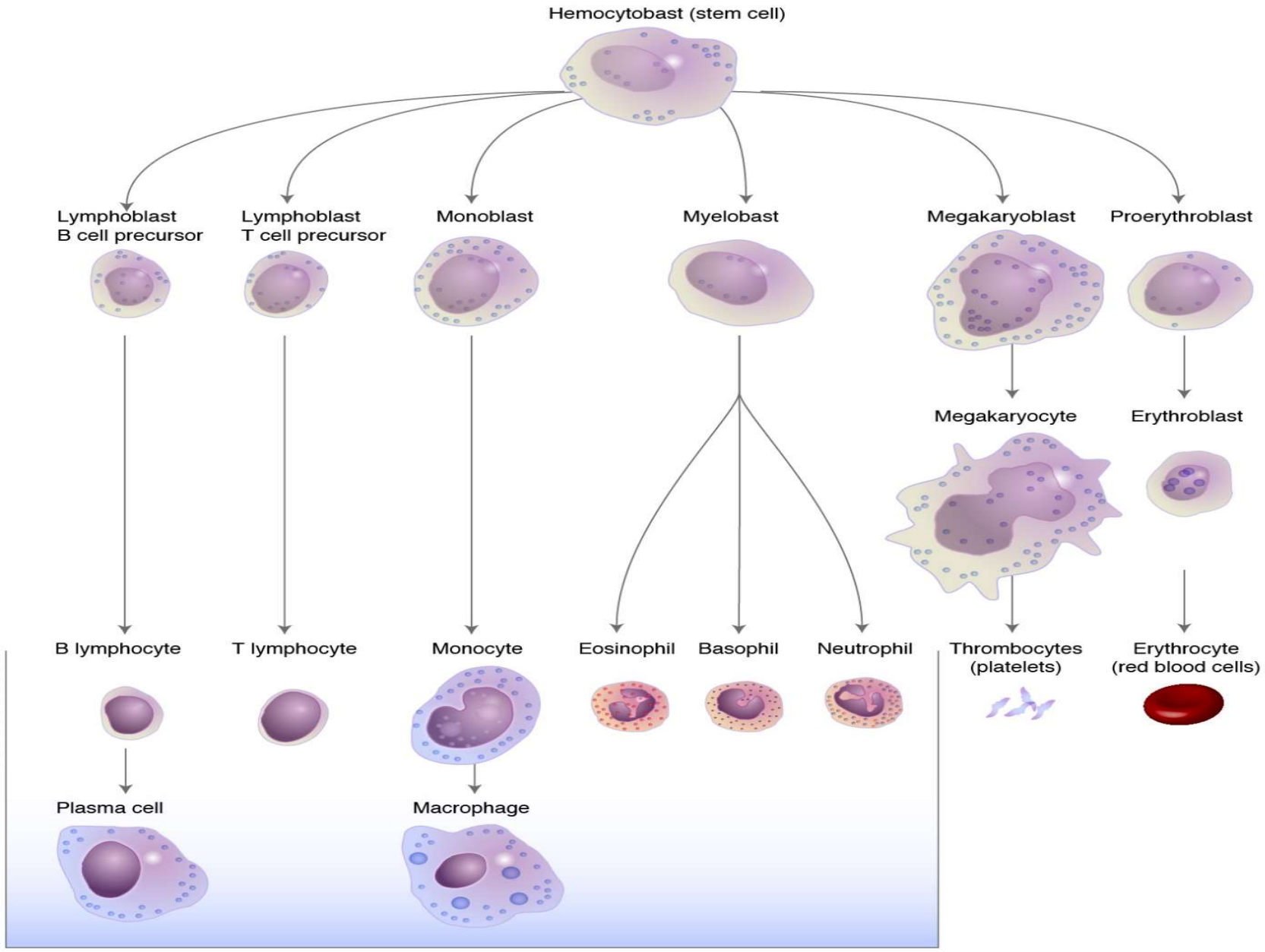
Immunity Concepts

- Acquired immunity: Active vs passive
  * Active: Person is exposed to foreign substance and immune system responds
  * Passive: Antibodies are transferred from person to person
- Acquired immunity: Natural vs artificial
  * Natural: Acquired by exposure to foreign substance
  * Artificial: Acquired by introduction of antigens or antibodies

Immunity Concepts

Type	Example
Naturally acquired active	Exposure to measles
Naturally acquired passive	Transplacental transfer
Artificially acquired active	Vaccinations or immunizations
Artificially acquired passive (introduction of antibodies)	Infusion of gammaglobulins



Lymphocytes - white blood cells

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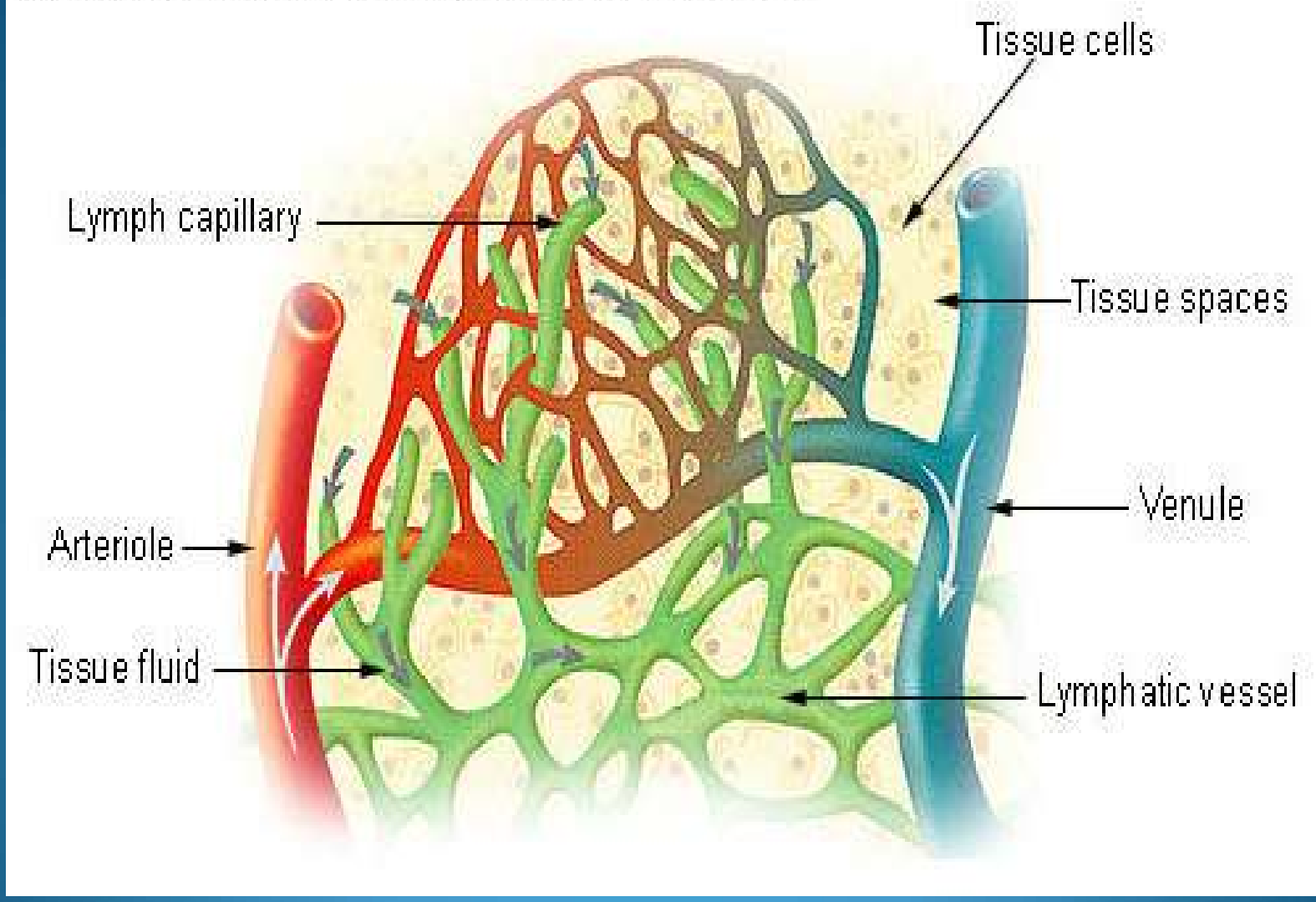
Humoral Immunity

- Antibody-mediated immunity
- Production of antibodies that act against foreign substance or organism
- These antibodies (proteins) are found in extracellular fluid including plasma, lymph or mucus secretions
- B cells or lymphocytes (white blood cells) are responsible for producing antibodies
- Primarily defends against bacteria, bacterial toxins and viruses

Lymph Capillaries in the Tissue Spaces



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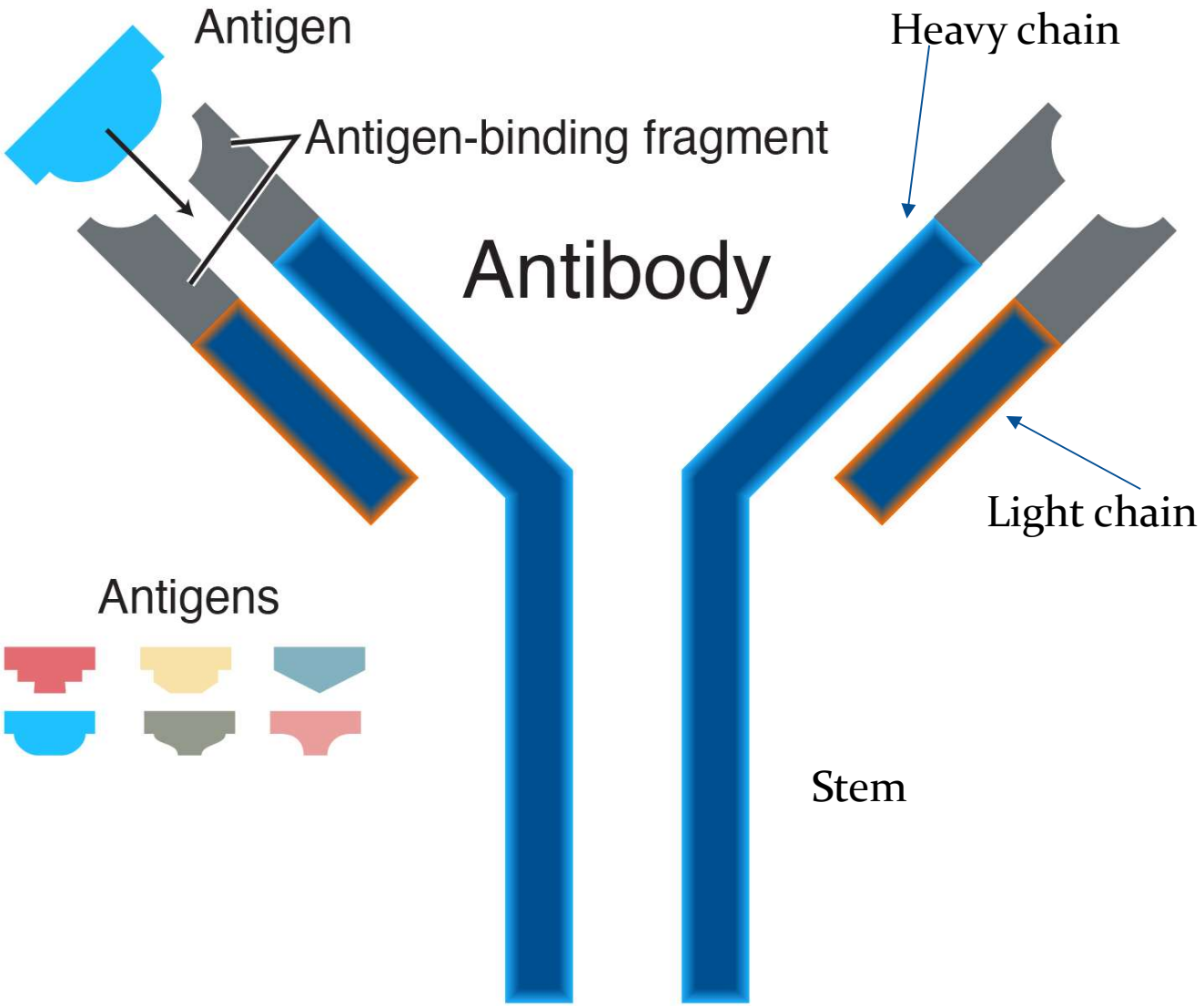
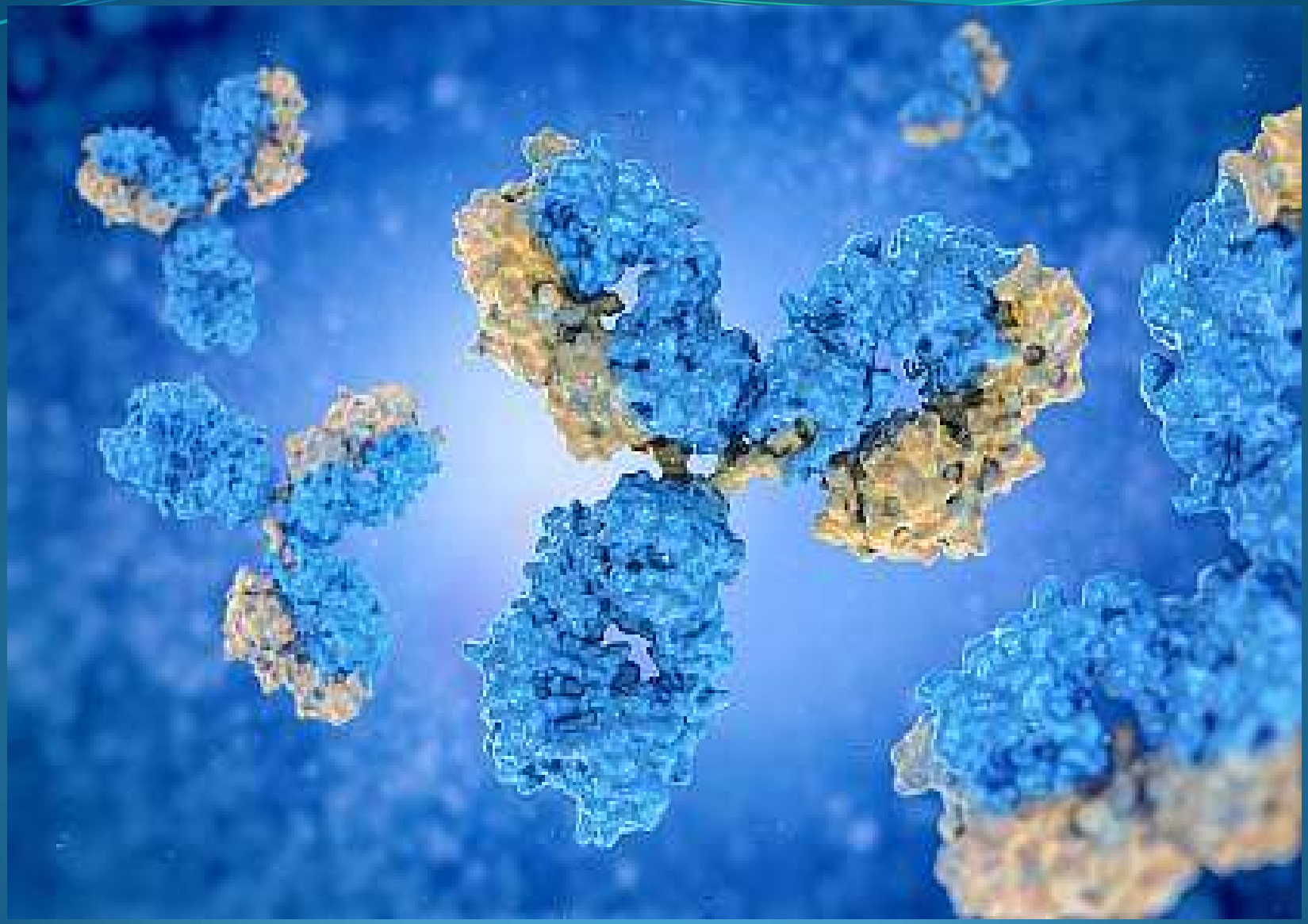
Cellular Immunity

- Cell mediated immunity
- Involves T cells or lymphocytes that respond to foreign substances or tissue
- Regulate activation and proliferation of other immune cells (especially Helper T cells)
- Effective against bacterial and viral infections *within* phagocytic or infected host cells
- Primary responder to transplanted tissues

Antigens

- "Non self"
- Usually proteins or large polysaccharides
- Antigenic compounds are usually components of invading microbes ie cell wall, capsule, flagella or toxin
- Nonmicrobial antigen include pollen, serum proteins from other individuals, surface molecules of transplanted tissue
- Areas for specific interactions with antibodies are called antigenic determinants or epitopes
- Nature of interaction is dependent of size, shape, chemical structure of antigens


Antigen
Heavy chain
Antigen-binding fragment
Antibody
Light chain
Antigens
Stem
www.nih.gov



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Antibody

- Proteins (immunoglobulins) that are produced in response to an antigen to neutralize or destroy antigen
- Highly specific
- Bacteria or viruses will have more than one antigenic determinant site (epitope) leading to multiple antibodies formed
- Each antibody has at least two identical sites to bind with antigen (ie “Y” form)

Antigen-Antibody Binding

- Interaction is rapid to form *antigen-antibody complex*
- Complex is now tagged for destruction by phagocytes or complement

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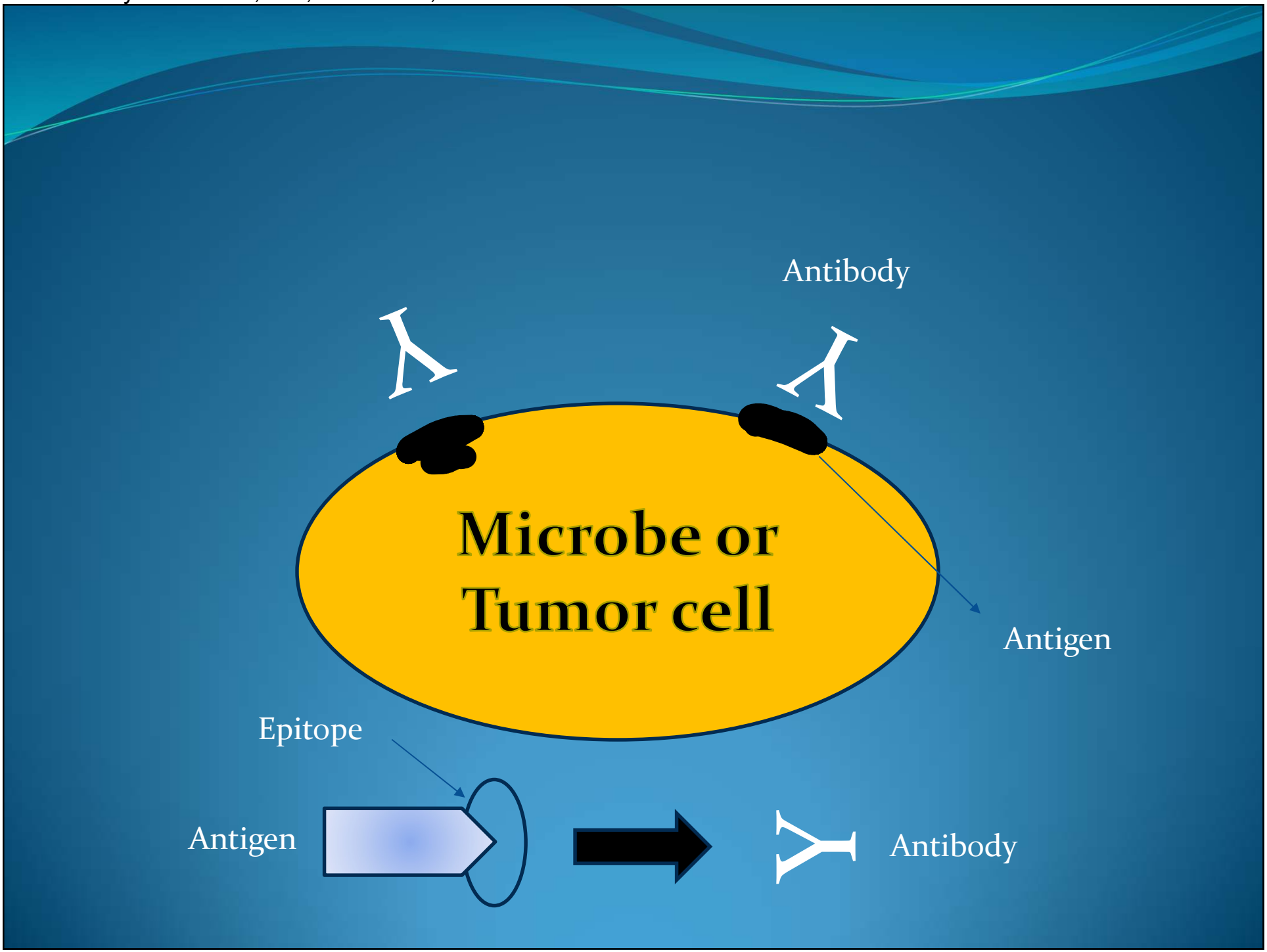
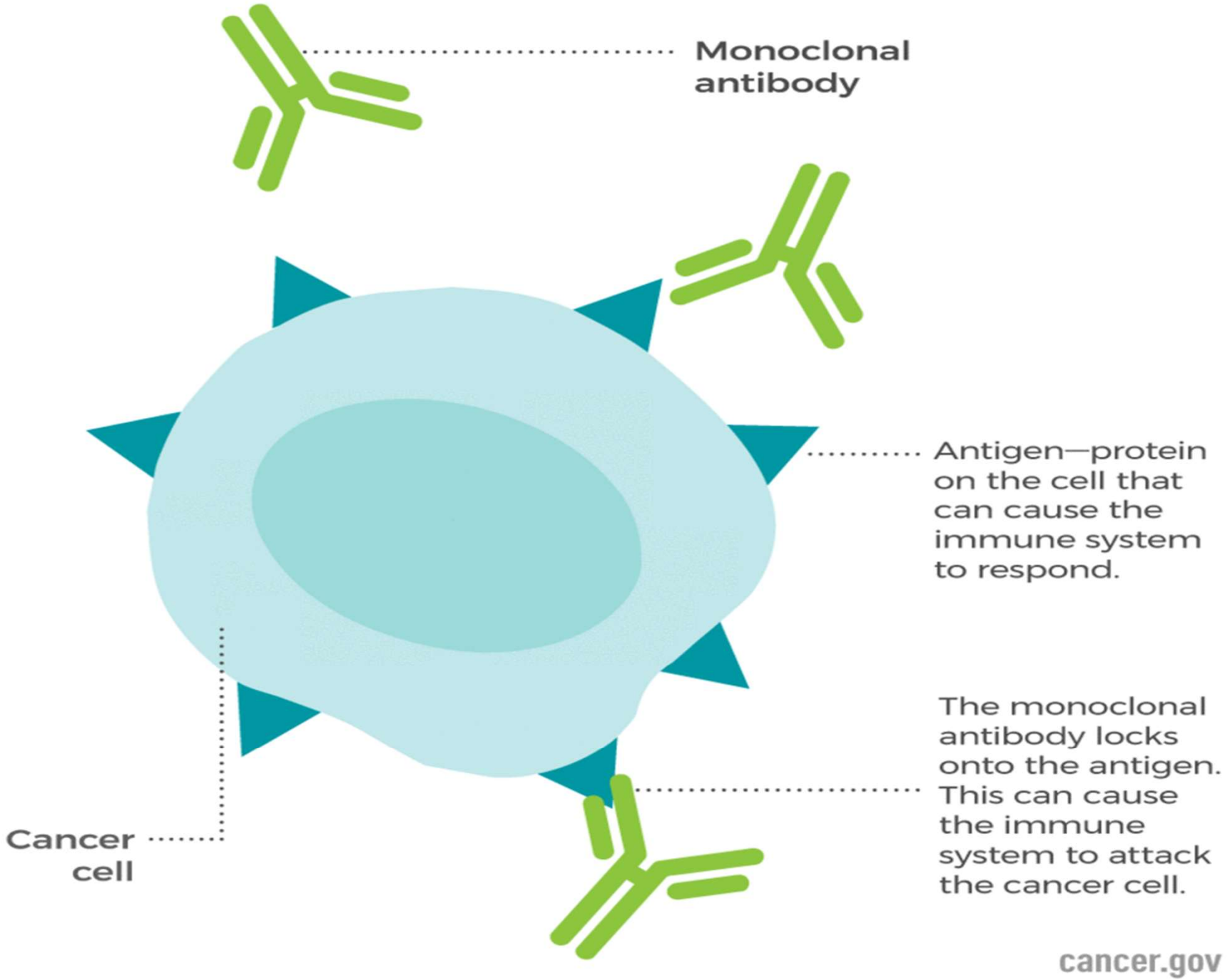
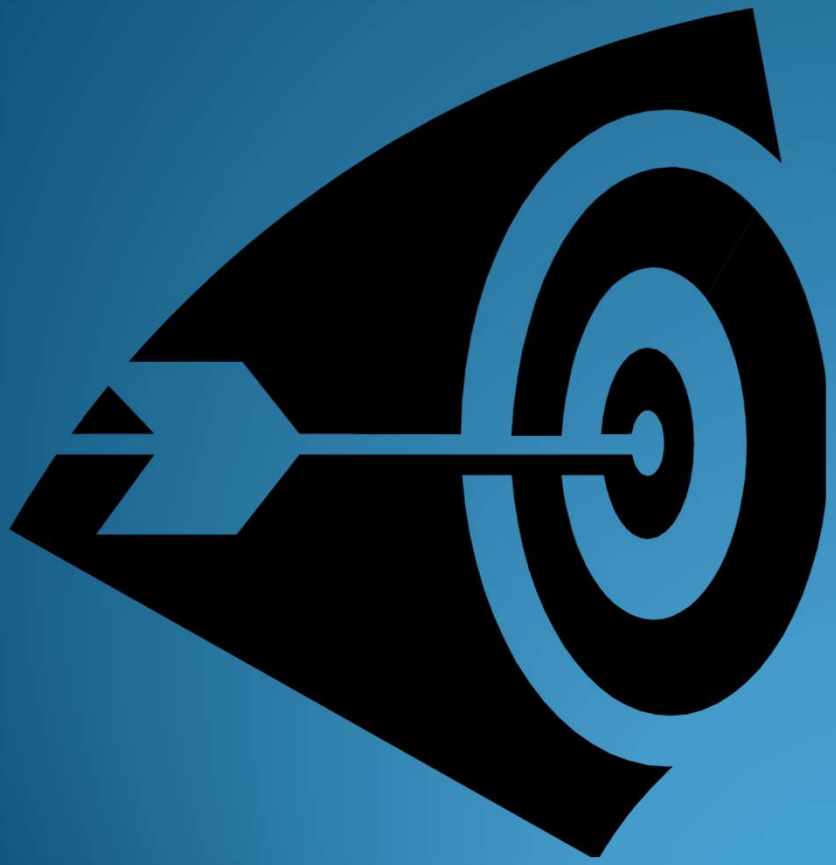

Antibody
Microbe or
Tumor cell
Antigen
Epitope
Antigen
Antibody


Monoclonal antibody
Antigen—protein on the cell that can cause the immune system to respond.
The monoclonal antibody locks onto the antigen. This can cause the immune system to attack the cancer cell.
Cancer cell
cancer.gov

Antigen-Antibody Binding



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- Agglutination (“carry”)
- Opsonization (“coat”)
- Neutralization (“surround”)
- Activation of complement (“lysis”)
- Inflammation (“disrupt)
- Antibody-dependent cell-mediated cytotoxicity (“attack”)

Complement Activation

Endothelial cell

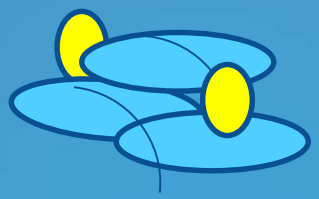
MAC
C_5

Complement activation

Leukocyte activated
Neutrophils recruited
Adhesion
NET formation
Cytokine release

Platelet activation

Thrombus Formation



Adapted from Afzali et al 2022

Monoclonal Antibodies (mAbs)

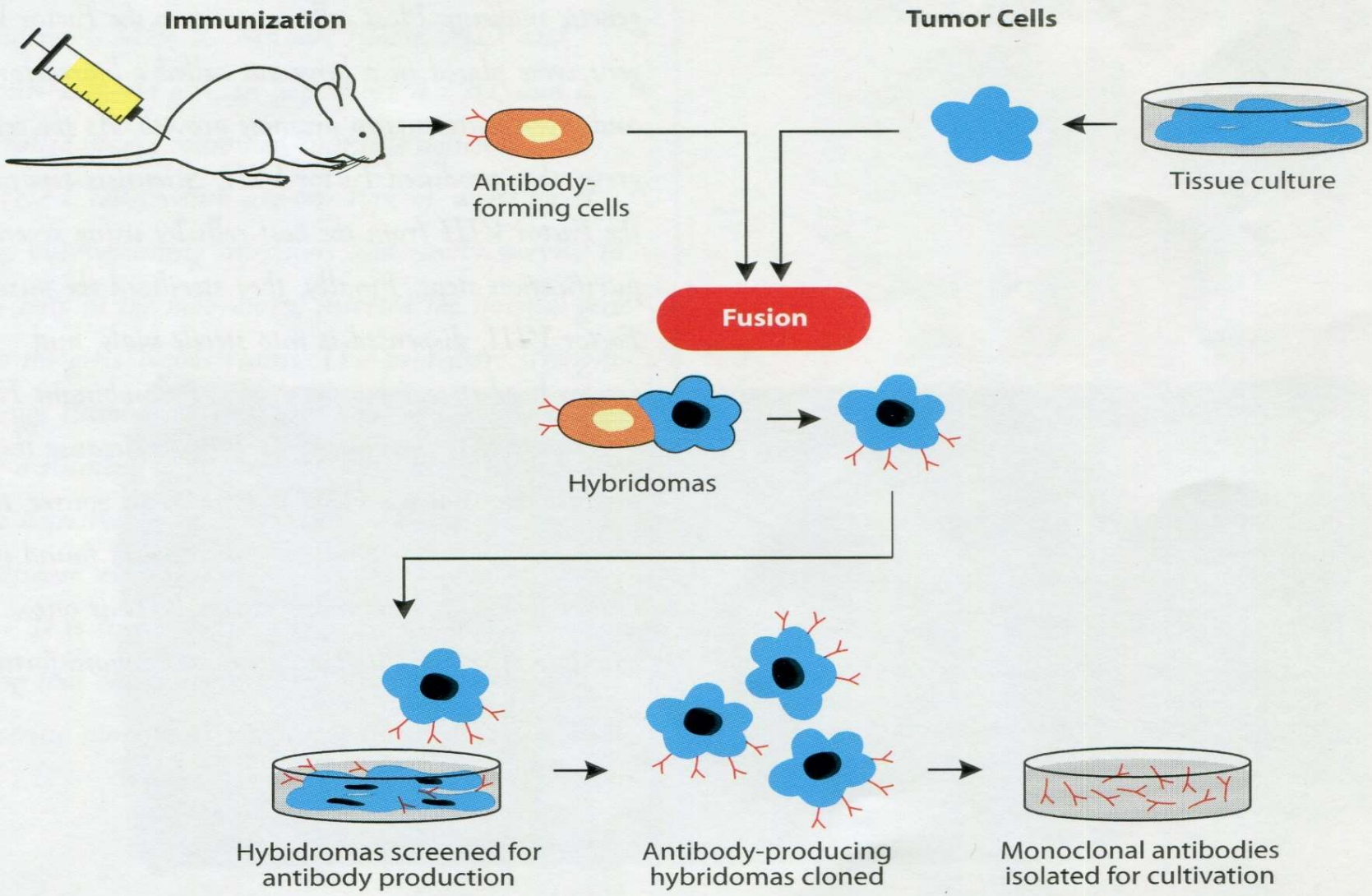
Historical Perspective

- "Targeted therapy"
- More efficacy and less toxicity
- Developed in 1975 when murine hybridoma methodology was first described
- First used to treat lymphoma in 1980
- "Ideal" antigen is one that is densely expressed on malignant cells but ***NOT*** on normal cells

Hybridoma Methodology

- Mimicking the introduction of an infection (antigen) to produce antibody producing B cells
- Able to grow cancer cells; "immortal"
- In 1984, scientists discovered a method to prolong the life of antibody producing B cells
- The "clones" of the original cell had the same antibody characteristics
- Fusion of the cancer cell and the antibody producing B cell = hybridoma
- Produced by single hybridoma clone = monoclonal antibodies

Monoclonal Antibody Production



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Types of mAbs

- Murine: Developed from foreign murine proteins
- Chimeric: Add human antibodies; 65% human
- Humanized: Add human antibodies where murine is antigen binding sites; 95% is human
- Human: Fully human

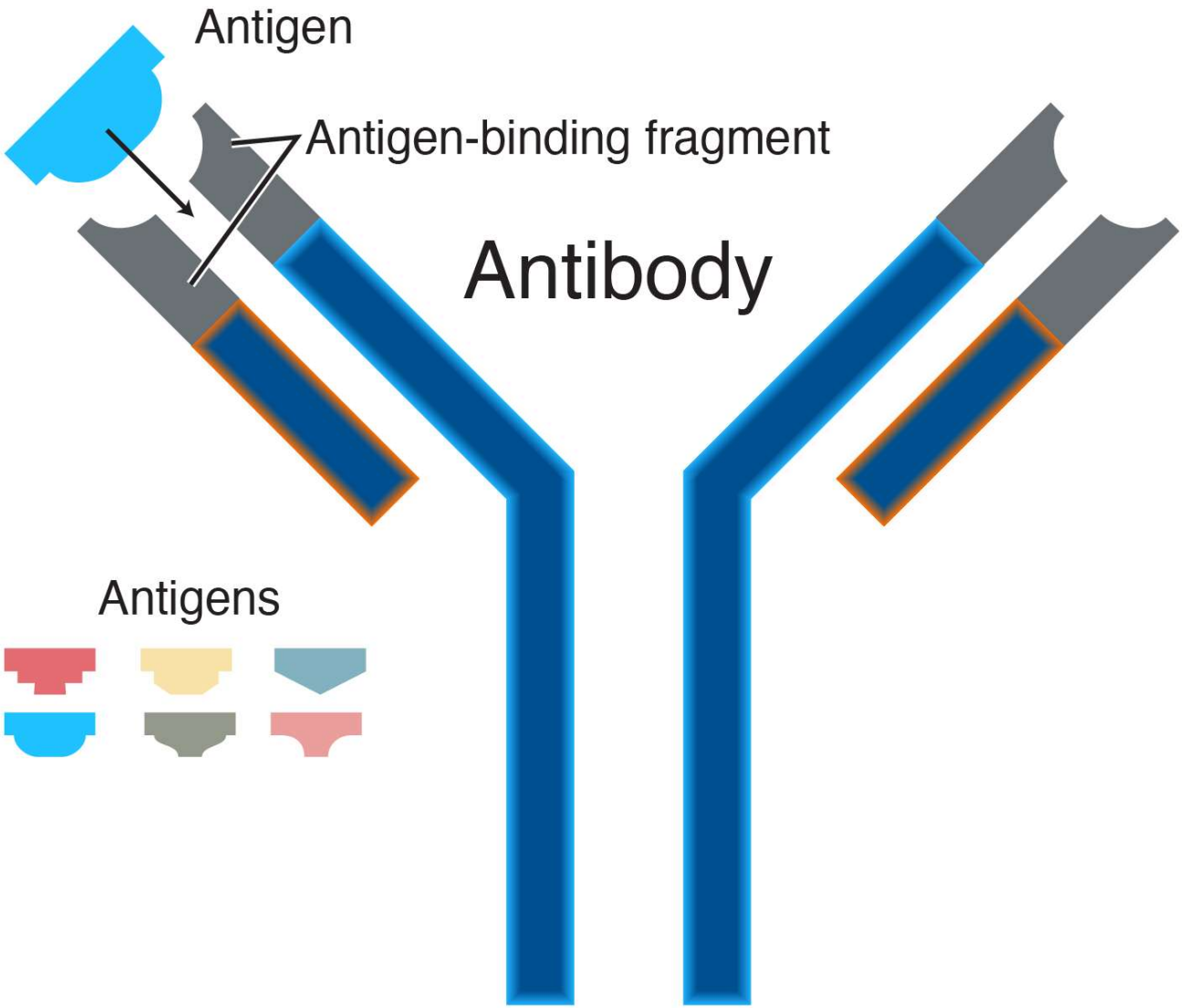
Personal photo

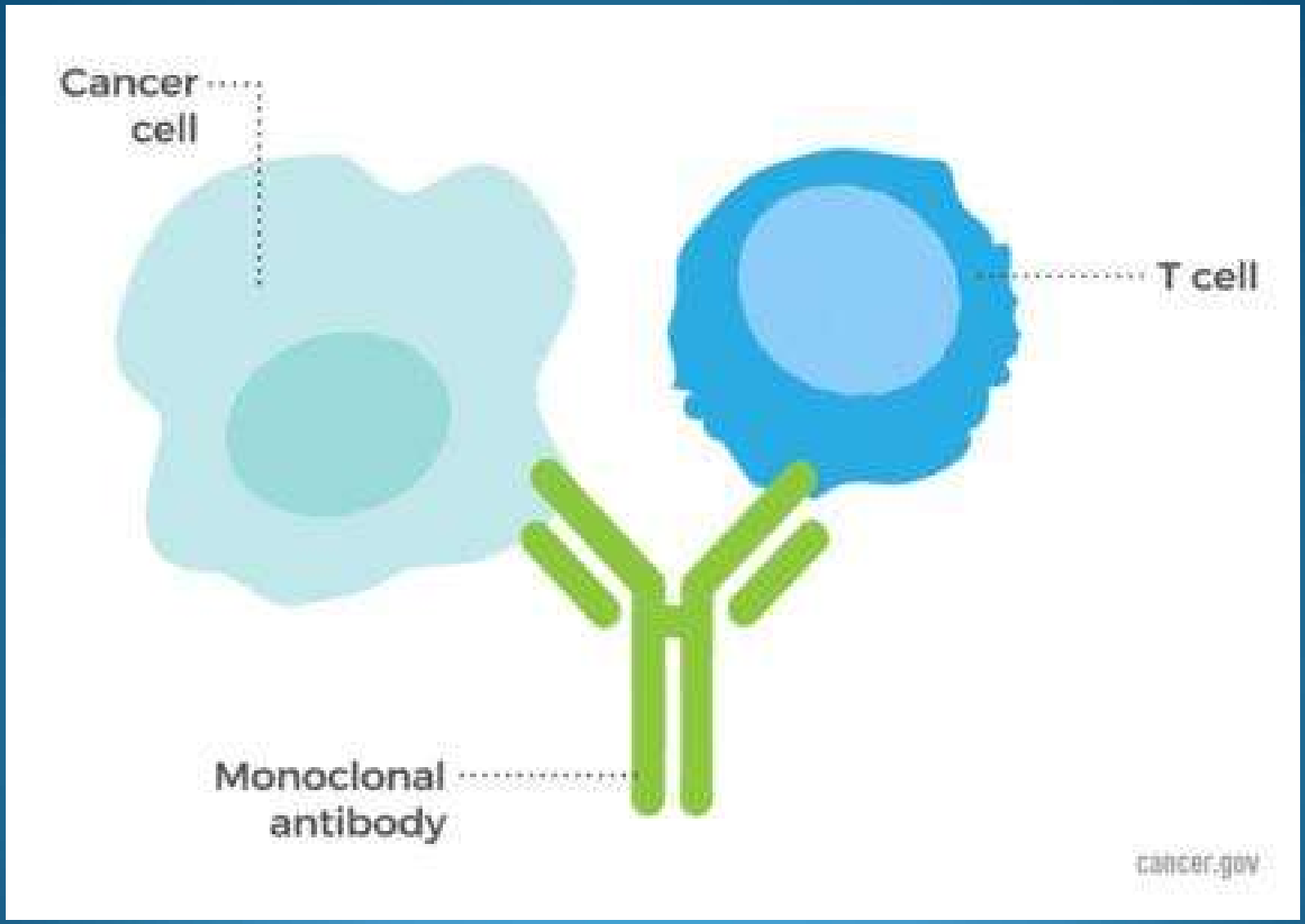
Nomenclature for mAbs

"mab (ends in)"

-omab	Murine
-ximab	Chimeric
-zumab	Humanized
-umab	Human

WHO International Nonproprietary Names


Antigen
Antigen-binding fragment
Antibody
Antigens
www.nih.gov


Cancer cell
T cell
Monoclonal antibody
cancer.gov

Mechanism of Action for mAbs

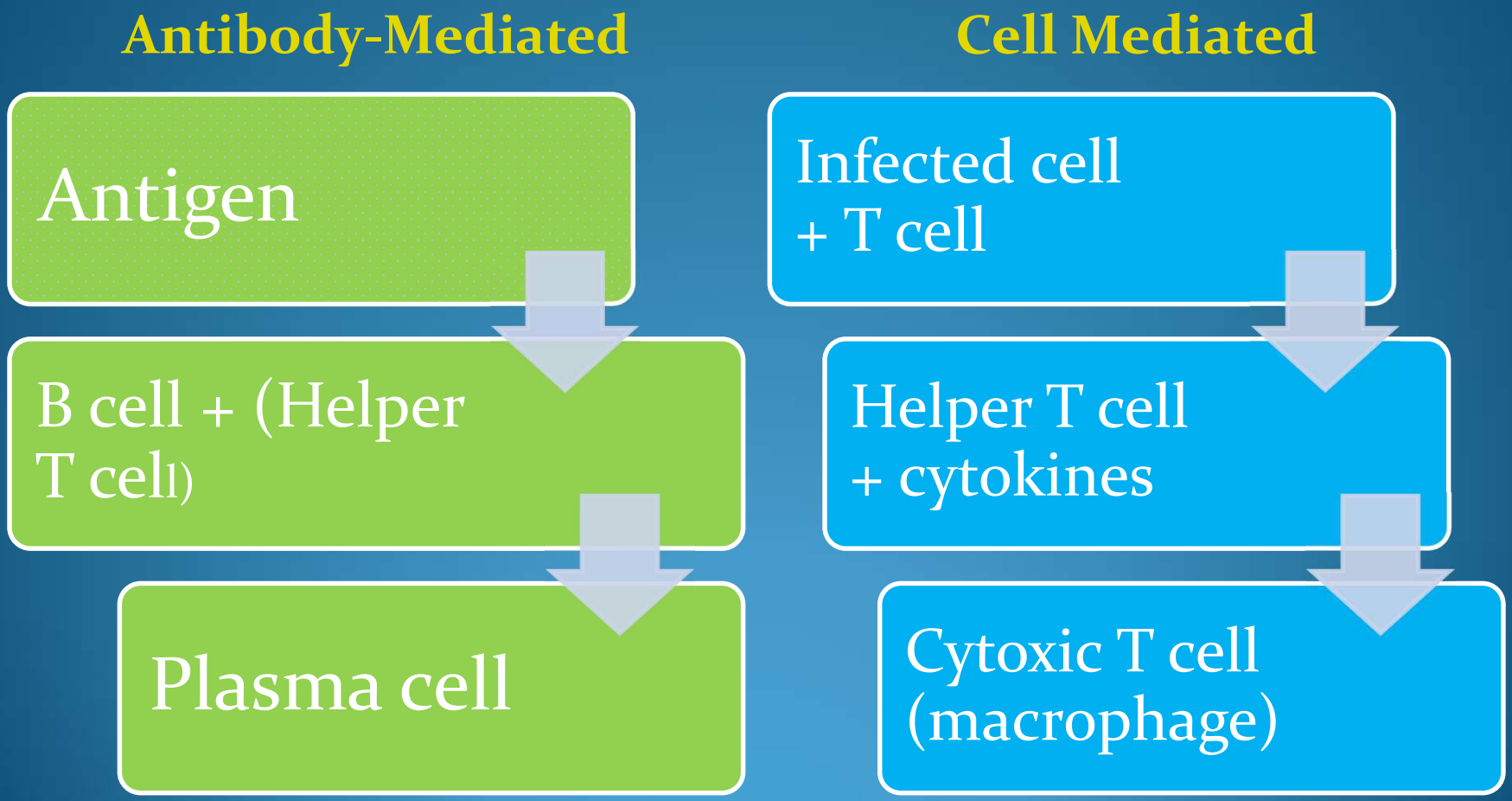
- Direct tumor cell killing
  * Stimulated by receptor agonist activity
  * Stimulated by receptor antagonist activity
- Immune-mediated tumor cell killing
  * Phagocytosis
  * Complement activation
  * Various T cell activation methods
- Vascular and stromal cell ablation
  * Vasculature receptor antagonism
  * Delivery of toxin to stromal cells
  * Delivery of toxin to vasculature

Bayer 2019

Interaction with T Cells

- T Cells
  * Classified by function
  * Classified by clusters of differentiation
- Clusters of differentiation (CD)
  * Classified on the type of cell surface molecules or receptor
  * Most common is CD4 (helper) or CD8 (cytotoxic)
- Relationship between B cells and T cells
  * B cell requires stimulation by a T cell when antigen is intracellular
- Conjugation of mAbs
  * Antibody that has a radioactive isotope or toxin incorporated into the constant region of the protein to kill specific cell; ***immunotoxin***

Immune System Interaction



mAbs:

Oncologic/Hematologic Diseases

Acute Leukemias

- Alemtuzumab
  * Leukemia; also used with multiple sclerosis
  * Target is CD52 antigen on leukemia cells
  * Dosing: IV initial dose 3 mg over 2 hrs daily up to 30 mg daily as tolerated
- Gemtuzumab ozogamicin
  * Acute myelogenous leukemia
  * Target is CD33 antigen on leukemia cells
  * Induction: 3 mg/m2 (maximum: 4.5 mg/dose) on days 1, 4, & 7 (in combination with daunorubicin & cytarabine)

Lymphoproliferative Disorders

- Rituximab (Rituxan)
  * First mAb developed for use in cancer
  * Target antigen is CD 20
  * Antibody dependent cell mediated cytotoxicity and complement dependent cytotoxicity
  * Diffuse large B cell lymphoma (DLBCL)
  * Used with cyclophosphomide, hydroxydaunorubicin (doxirubicin), vincristine (oncovin) and prednisone (CHOP)
  * R-CHOP

Lymphoproliferative Disorders

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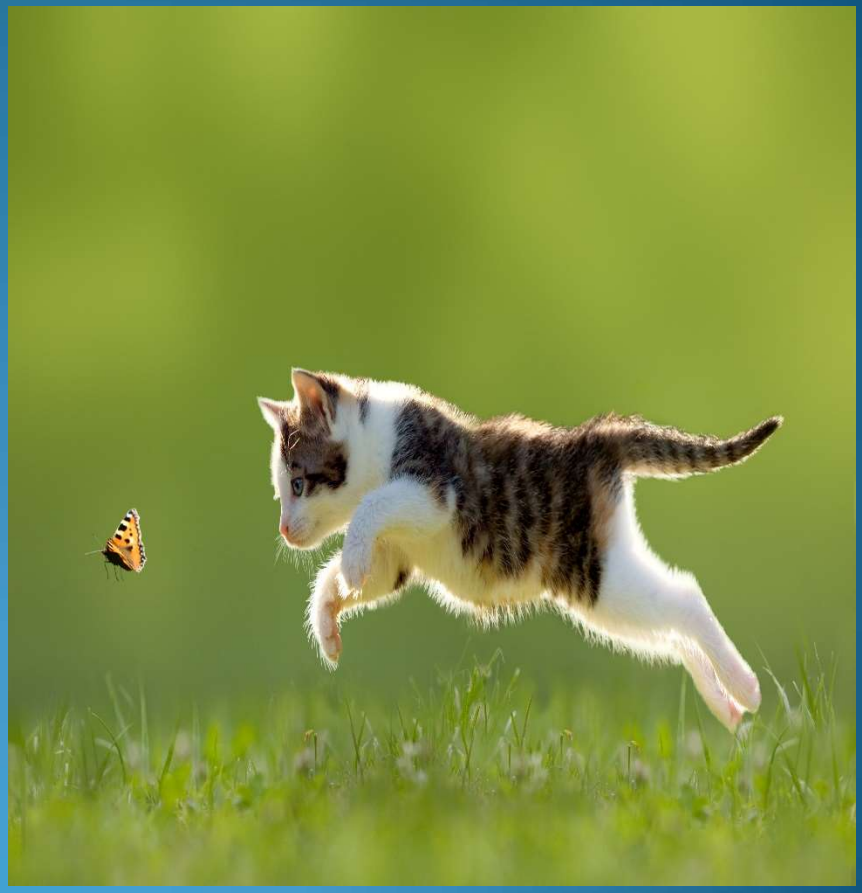
- Dosing for rituximab
  * 250-375 mg/m² at varying intervals based protocol and disease process
- Caution in patients with cardiac and pulmonary disease
- Tumor lysis syndrome
- Skin reactions

Lymphoproliferative Disorders

- Alemtuzumab (campath)
  * Used with chronic lymphocytic leukemia (CLL)
  * Targeted antigen is CD52
  * Destroys target cells by complement and/or antibody dependent cellular cytotoxicity
  * Induces direct apoptosis
  * Could be monotherapy if failure with fludarabine
  * Usually used earlier in disease course

Lymphoproliferative Disorders

- Dosing for alemtuzumab
  * Starting dose is 3 mg/day
  * Escalate to 30 mg/day 3 times per week
  * Varying frequencies dependent on stage of disease
- Caution with pancytopenia
- Caution with infection



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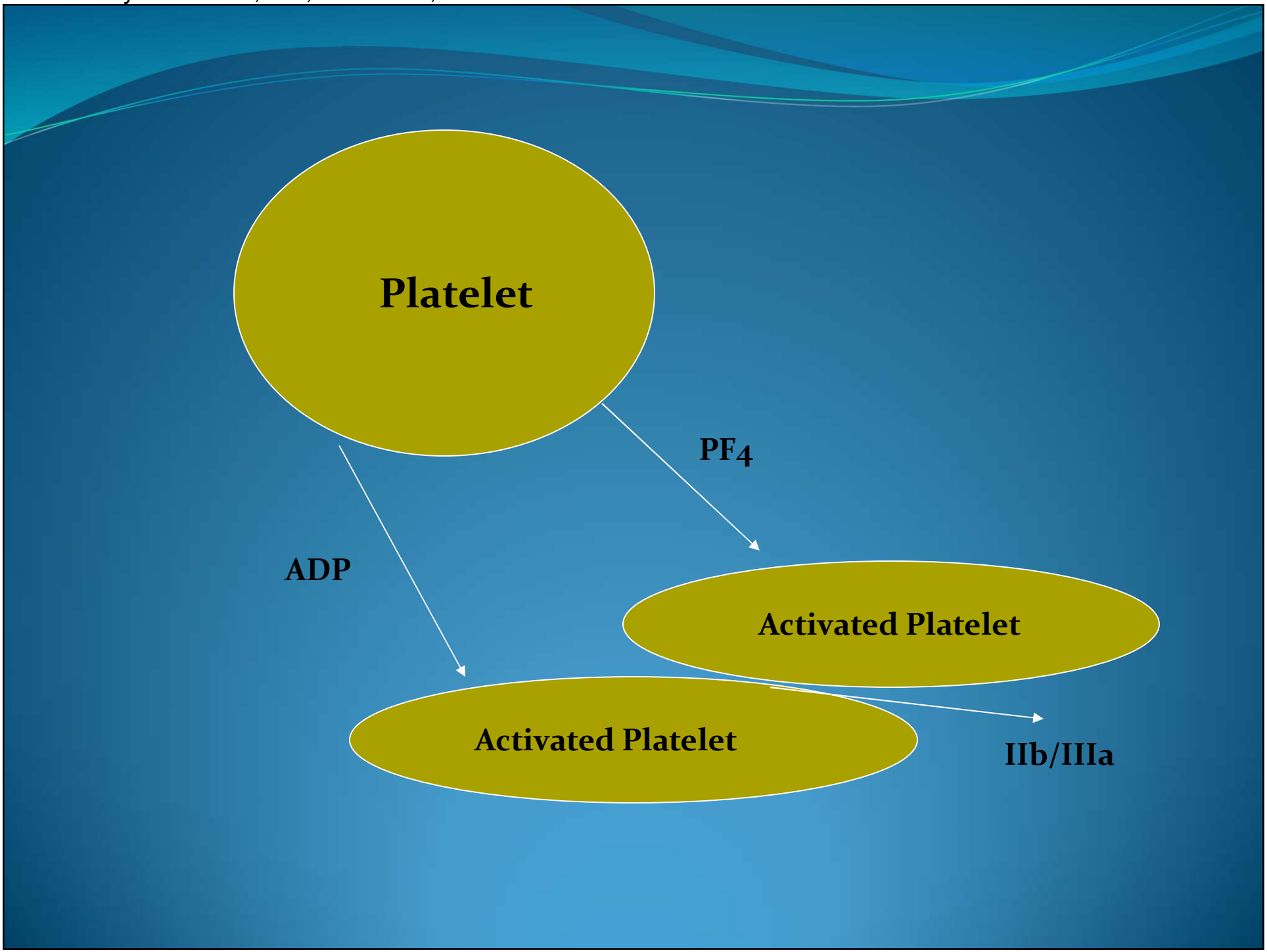
mAbs for Other Cancers

- Colorectal cancer
  * Bevacizumab (Avastin):
  * Inhibits vascular endothelial growth factor(VEGF)
  * Dose range dependent on disease 5 – 15 mg/kg every 2 weeks
- Breast cancer
  * Trastuzumab (Herceptin)
  * Targets HER2/neu receptor (overexpression)
  * Dosing: 4 mg/kg loading dose and 2 mg/kg weekly dose

mAbs:
Other Disease Processes

mAbs for Cardiac Disease

- Cardiac disease
  * Target antiplatelet mechanisms
- Abciximab (reopro)
  * Glycoprotein IIb/IIIa inhibitor at receptor site
  * GP receptor site pivotal for adherence and aggregation of platelets
  *Dosing: 0.15 - 0.3 mg/kg
  * Within 2 hrs, 80% receptor site disabled
  * Effect lasts up to 48 hrs


Platelet
PF4
ADP
Activated Platelet
Activated Platelet
IIb/IIIa

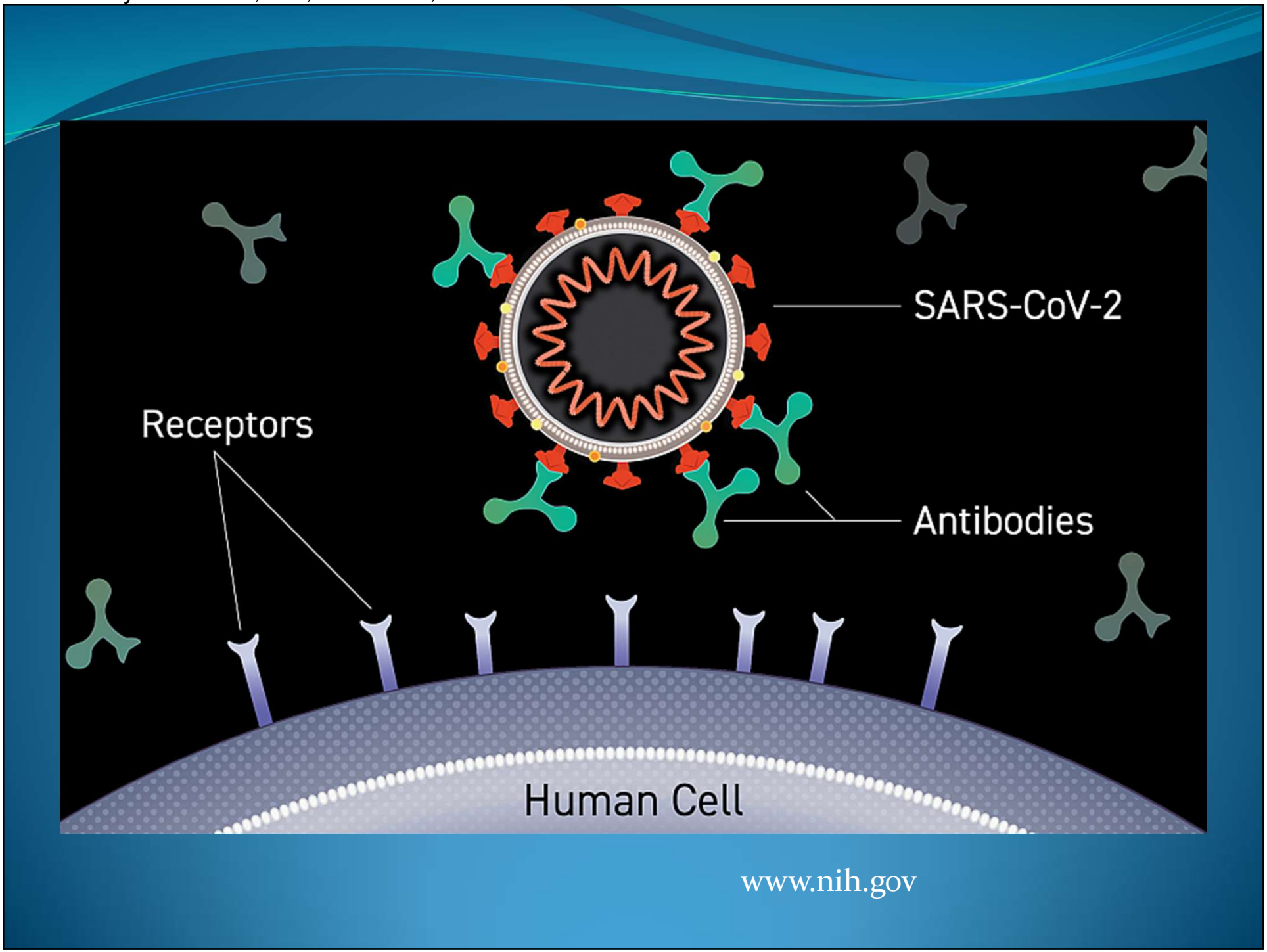
mAbs for Autoimmune Diseases

- Rheumatoid arthritis (RA)
  * Infliximab (Remicade)
  * Inhibits TNF α
  * Dosing: 3 mg/kg at 0, 2, 6 weeks
- Another mAb for RA
  * Tocilizumab
  * Target is IL-6 receptor
  * Dosing: 4 mg/kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks

mAbs and Other Diseases

- Pulmonary HTN
- Monoclonal antibody (IgG1)
- Inhibits migration of activated monocytes and macrophages
- Reduces pulmonary vascular remodeling and pulmonary artery pressure in pre-clinical rodent models of pulmonary arterial hypertension (PAH).

Personal photo


SARS-CoV-2
Receptors
Antibodies
Human Cell
www.nih.gov

mAbs for Infectious Diseases

- COVID 19 target
  * Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, Sotrovimab, and Bebtelovimab
  * **Not approved for use in US** because dominant Omicron subvariants not susceptible
- *Clostridium difficile* colitis target
  * Bezlotoxumab
- CD4 multidrug resistant HIV infection
  * Ibalizumab

"Cytokine Storm"

What Is the Real Name?

Cytokine Storm

Cytokine Release Syndrome (CRS)

Inflammation

Hemophagocytic Lymphohistiocytosis (HLH)

Immune Dysregulation

Definition?

Cytokine storm and CRS: "Life threatening systemic inflammatory syndromes involving elevated circulating cytokines and immune-cell hyperactivation that can be triggered by various therapies, pathogens, cancers, autoimmune conditions and monogenic disorders"

Fajgenbaum & June 2020 p. 2255

Common Theme

"Recognition that the immune response to a pathogen, but not the pathogen itself, can contribute to multiorgan dysfunction"

Fajgenbaum & June 2020 p. 2255

Clinical Causes of Cytokine Storm

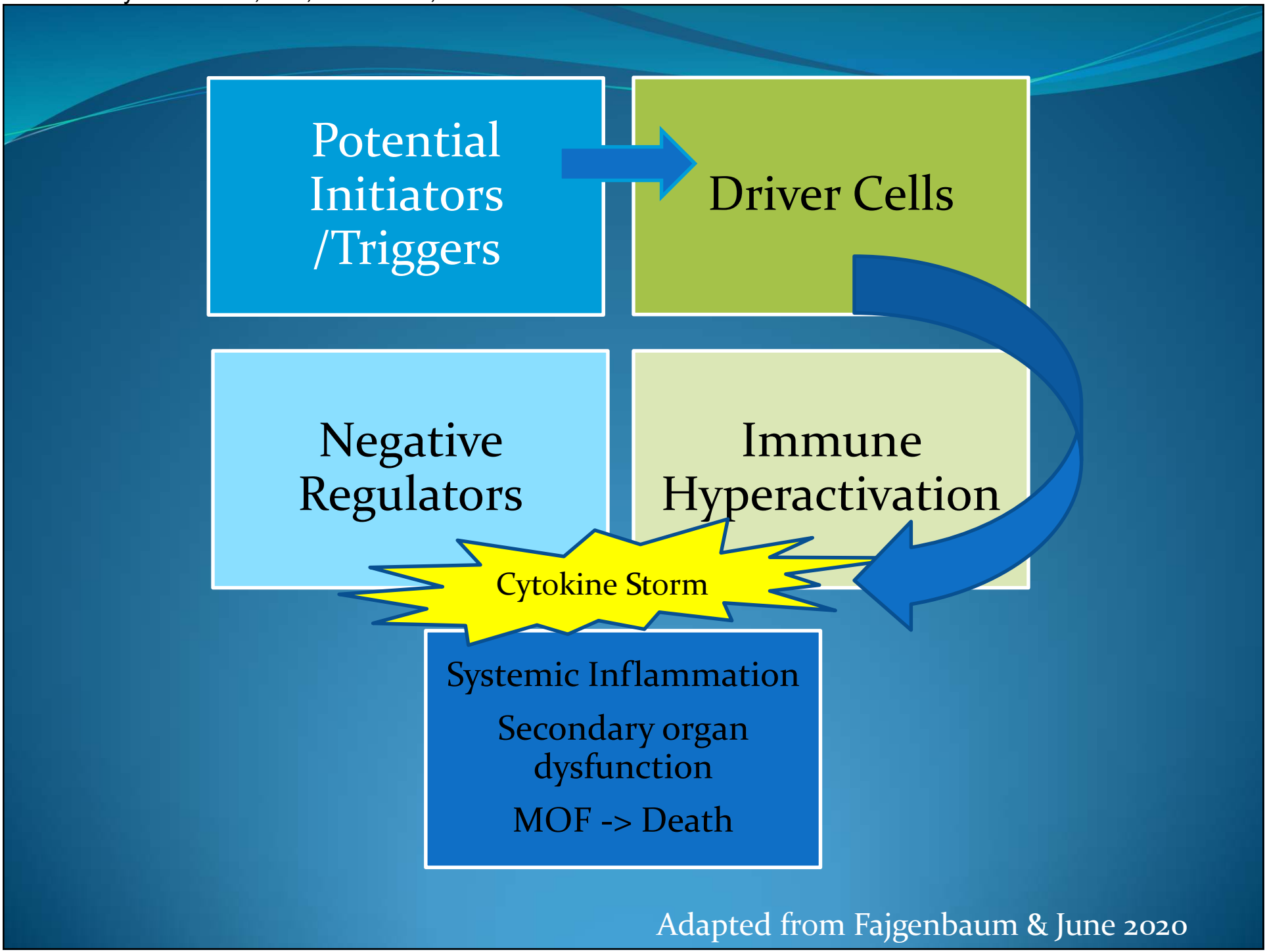
Type of Cytokine Storm	Cause	Cellular or Cytokine Driver
Iatrogenic		
CAR T cell therapy	Infusion of CAR T cells	Macrophages, IL6, IL 1β
Blinatumomab	Infusion CD19 & CD3 T cell receptor antibody	Activated T cells, macrophages, IL6
Pathogen-induced		
Bacterial sepsis	Hematogenous bacterial infections	Multifactorial drivers
EBV-associated HLH	EBV infection	Interferon γ, TNF, CD8+ T cells
HHV-8-assoicated MCD	HHV-8 infection in HIV pt	Viral IL6, IL6
COVID-19	SARS-CoV-2 infection	Unknown

Adapted from Faigenbaum & June 2020 p. 2262

Clinical Causes of Cytokine Storm

Type of Cytokine Storm	Cause	Cellular or Cytoine Driver
Monogenic/autoimmune		
Primary HLH	Germline mutation	CD8+ T cells, interferon γ
Secondary HLH or MAS	Viral cause (EBV or CMV)	CD8+ T cells, interferon γ IL 1β
Autoinflammatory disorders	Germline mutation in genes associated with innate immune system	Innate cells, TNF, IL 1β
Idiopathic MCD	Unknown cause	IL6, activated T cells

Adapted from Fajgenbaum & June 2020 p. 2262



Adapted from Fajgenbaum & June 2020

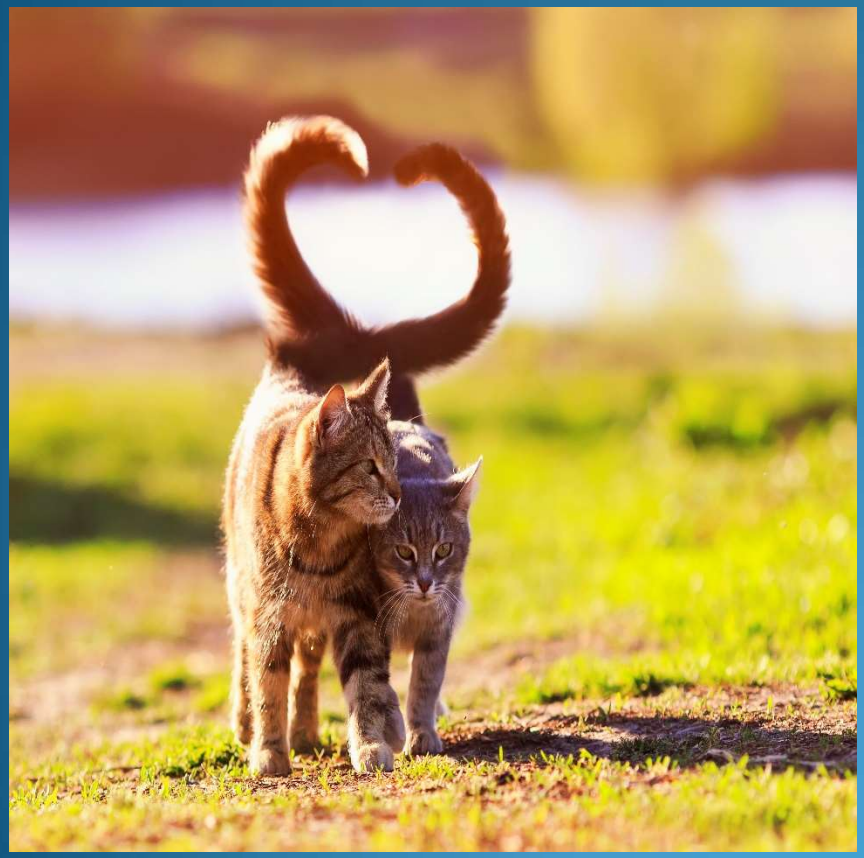
Mediators of Cytokine Storm

- Cytokines and growth factors
  * Interleukins are cytokines that serve as communicators between WBCs
  * IL-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-18, IL-33
  * Interferon-γ, TNF, GM-CSF, VEGF
- Chemokines are cytokines that induce migration of WBC into tissue
  * IL-8, MIG, IP-10, MCP-1, MIP-1α, MIP-1β
- Plasma proteins
  * CRP, Complement, Ferritin

Clinical Presentation

- Hypersensitivity reaction: Range of reactions according to type of reaction; "infusion reactions" and is considered immunopathology
- Common terminology criteria of adverse events (CTCAE)
- Clinical presentation
  - * Fever and/or shaking chills
  - * Flushing and/or itching
  - * Alterations in heart rate and BP
  - * Dyspnea or chest discomfort
  - * Abdominal pain, nausea, vomiting

Types of Allergic Reactions



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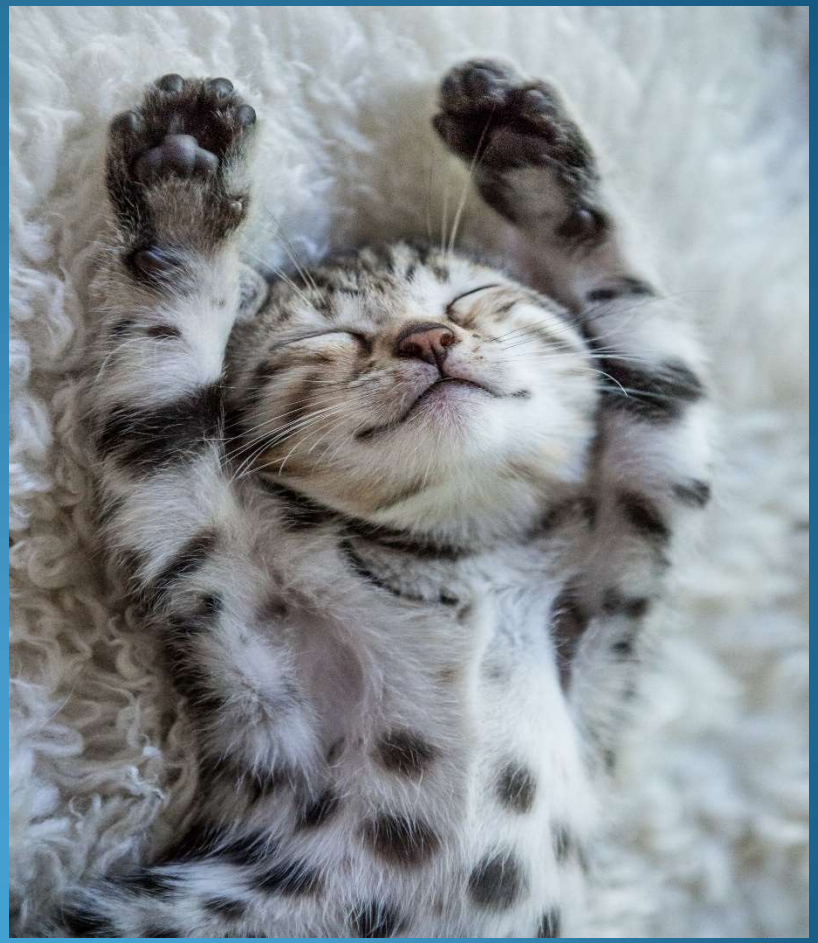
- Type I: Allergy
- Type II: Cytotoxic (antibody dependent)
- Type III: Immune complex
- Type IV: Delayed hypersensitivity (antibody independent)

Management of Side Effects

- Managing anaphylaxis
  * Anticipate: Acetaminophen and diphenhydramine
  * Anaphylaxis
    - Diphenhydramine
    - H2 antagonist
    - Steroids
    - Epinephrine
  * Fluid resuscitation
  * Vasoactive support
- Pre-emptive management
  * Infusion rate
  * Dose fractionation

Long Term Side Effects

- Immunosuppression
- Destruction of WBC, especially neutrophils
- Varying impact on WBC depending on drug



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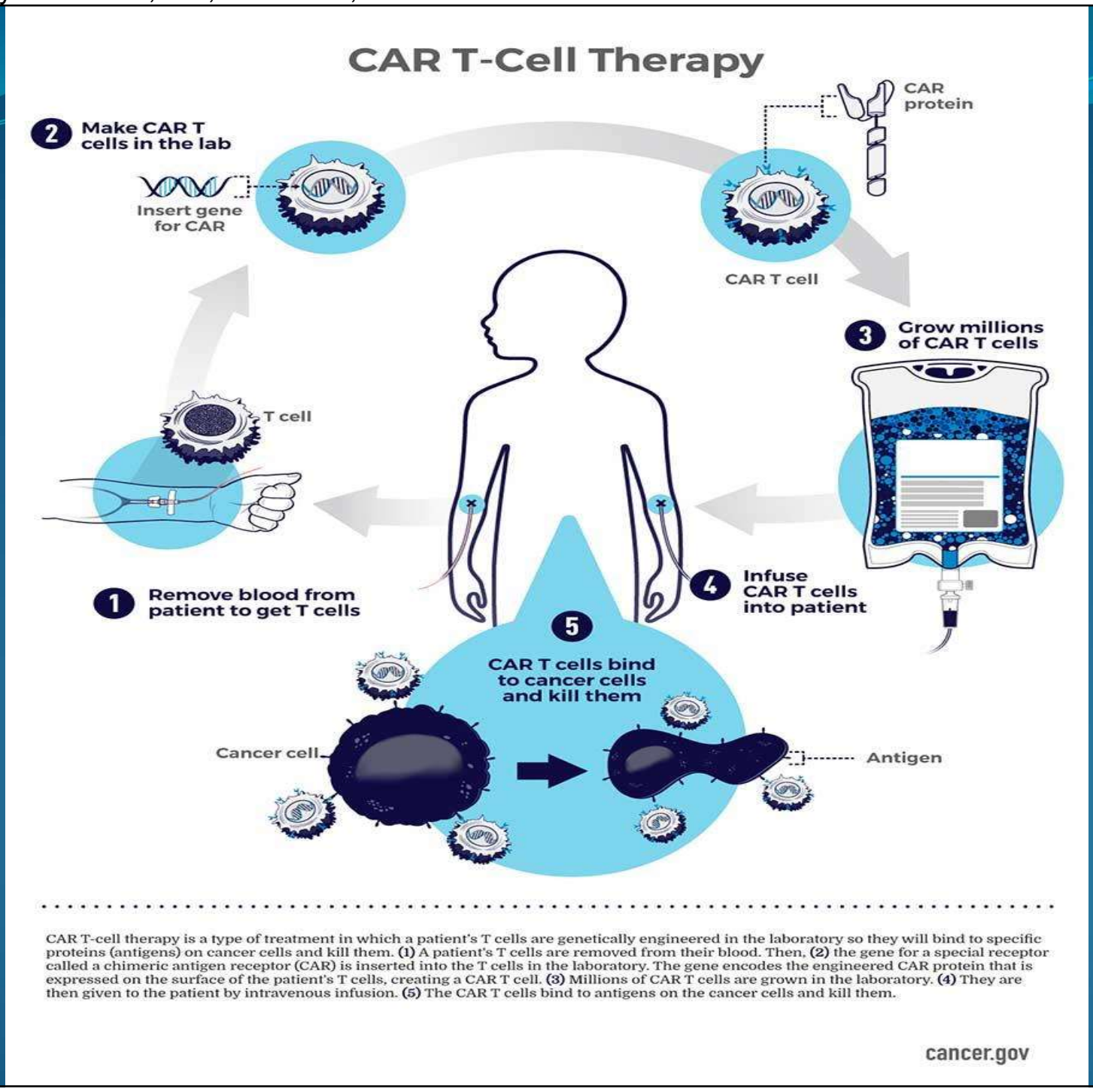
CAR T-Cell Therapy
2 Make CAR T cells in the lab
Insert gene for CAR
CAR protein
CAR T cell
3 Grow millions of CAR T cells
T cell
1 Remove blood from patient to get T cells
4 Infuse CAR T cells into patient
5
CAR T cells bind to cancer cells and kill them
Cancer cell
Antigen
CAR T-cell therapy is a type of treatment in which a patient's T cells are genetically engineered in the laboratory so they will bind to specific proteins (antigens) on cancer cells and kill them. (1) A patient's T cells are removed from their blood. Then, (2) the gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells in the laboratory. The gene encodes the engineered CAR protein that is expressed on the surface of the patient's T cells, creating a CAR T cell. (3) Millions of CAR T cells are grown in the laboratory. (4) They are then given to the patient by intravenous infusion. (5) The CAR T cells bind to antigens on the cancer cells and kill them.
cancer.gov

Case Studies

Case Study

- 36 yr old female with history of Jobs syndrome or Hyper IgE syndrome. She was found to have coronary artery aneurysms, especially right coronary artery. She has had 2 MIs due to aneurysms. She was treated with Abciximab (reopro) twice with success.

What do you think?

She had no side effects when she received Abciximab. She is currently on clopidogrel and will have to take it forever.

Case Study

- 46 yr old Korean male with history of severe aplastic anemia who also may have latent tuberculosis due to exposure to father who had active tuberculosis 10 years ago. He was admitted to NIH to participate in protocol which uses Rituximab as the initial therapy.

What do you think?

The ID consult team wanted the pulmonary consult service to see the patient and bronch him before starting rituximab. Why?


Personal photo

Summary

- "Targeted therapy"
- Best antigen is the key concept
- Antigen-antibody complex is preparation for destruction
- Expectation of allergic reaction
- Side effects of mAbs: Immunosuppression and risk of infection
- Great promise in the future

Contact me

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