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Immunotherapy: An Innovative Approach to Fighting Cancer

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Overview

Global Scope of Cancer & Current Trends

Treating Cancer: The Basics

Traditional Chemotherapy: A Brief History

Basic Overview of the Immune System

Immunotherapy: What is it & How it is Different?

Applications for Contemporary Cancer Care

Advantages & Disadvantages to Immunotherapy

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Summary

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Learning Objectives

1. Understand how cancer is changing globally, why it is important to detect cancer early when possible, how cancer care has evolved over time, and key historic breakthroughs in the science of cancer.
2. Develop an appreciation for our body's natural immune system, and its biological role with cancer.
3. Learn what immunotherapy is all about, how it is different than traditional chemotherapy, its advantages for cancer care, and areas for further research.

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DISCLAIMER:

This lecture is for general educational purposes only!

Every cancer is different, every person's biology and specific clinical situation is different, and there may be many factors that determine whether a patient is a good candidate (or not) for consideration of immunotherapy.

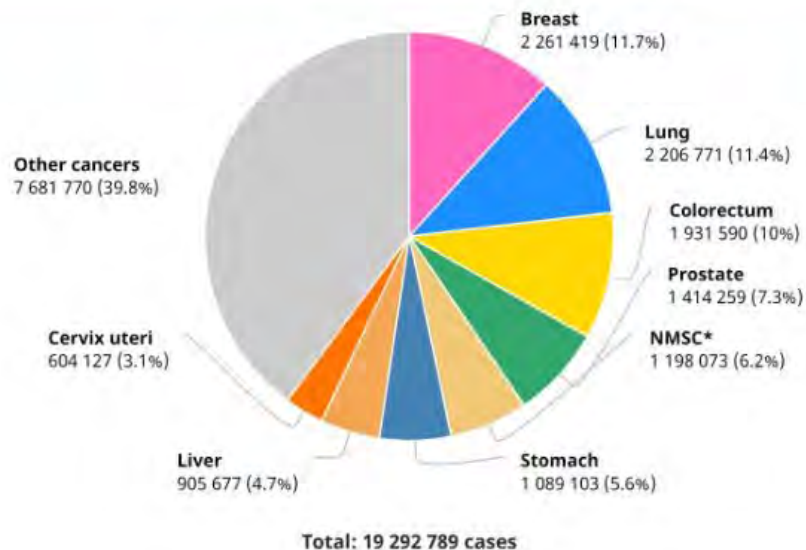
An in-depth discussion of the individual benefits or risks of immunotherapy, the specific indications (supported by national guidelines and evidence for each type and stage of cancer), and any contraindications or significant side-effects or complications related to the use of immunotherapy (or any related systemic cancer therapies) is beyond the scope of this lecture and is best reviewed in private consultation with a patient's personal qualified oncologic specialist.

- Cancer is a leading cause of death globally: Nearly 10 Million deaths in 2020 alone
- **Most Common Types:**
 - Lung (2.2M cases; 1.8M deaths)
 - Breast (2.2M cases; 685K deaths)
 - Colon & Rectal (1.9M cases; 916K deaths)
 - Also Prostate, Skin, Stomach, & Liver Cancers
- Increased risk of cancer with age, other medical conditions, and certain risk factors or exposures

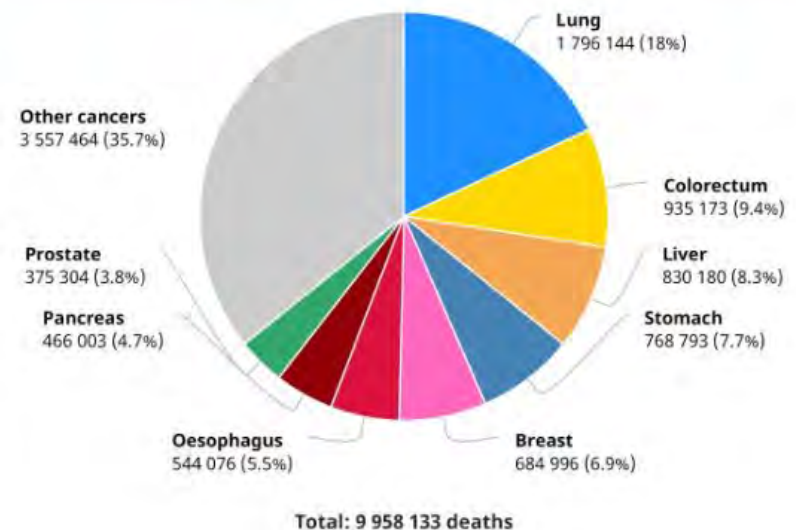


All cancers

Number of new cases in 2020, both sexes, all ages



Number of deaths in 2020, both sexes, all ages

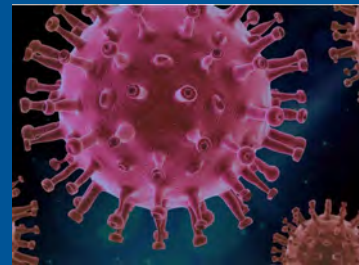


*Source: World Health Organization (WHO), Global Cancer Observatory, 2022.

Global Scope of Cancer (Cont.)

Causes of Cancer:

- Chemical carcinogens
- Physical carcinogens
- Biological carcinogens
- Genetic or hereditary
- Behavioral factors



UNITED STATES OF AMERICA

Cancer Country Profile 2020

BURDEN OF CANCER

Total population (2019)

329,064,917

Total # cancer cases
(2018)

2,129,118

Total # cancer deaths
(2018)

616,714

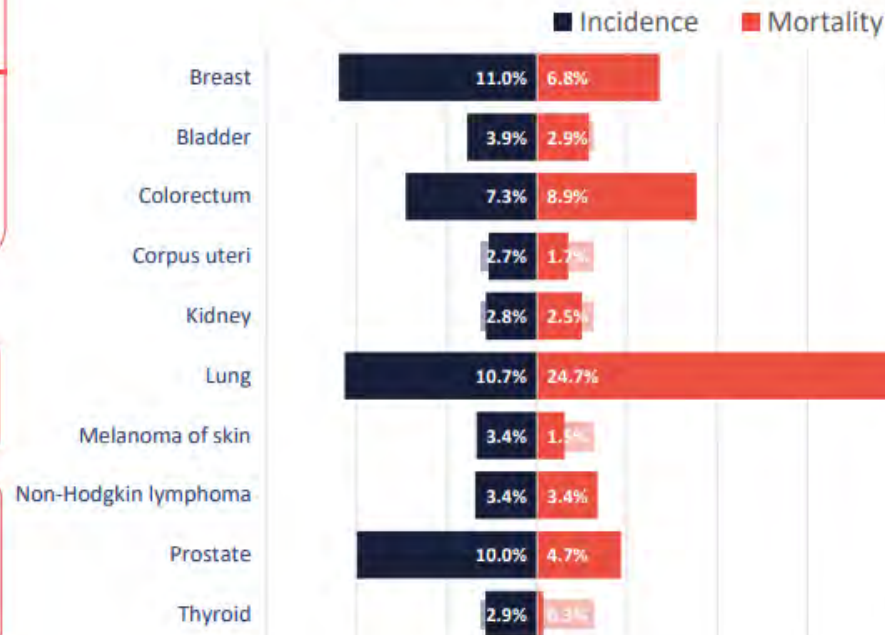
Premature deaths from NCDs (2016)

788,905

Cancer as % of NCD premature deaths (2016)

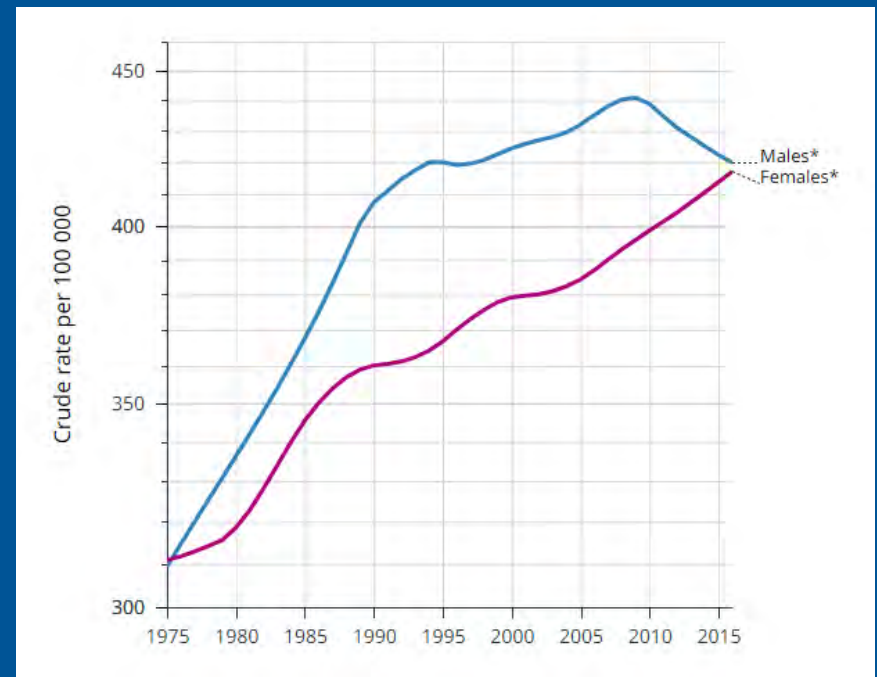
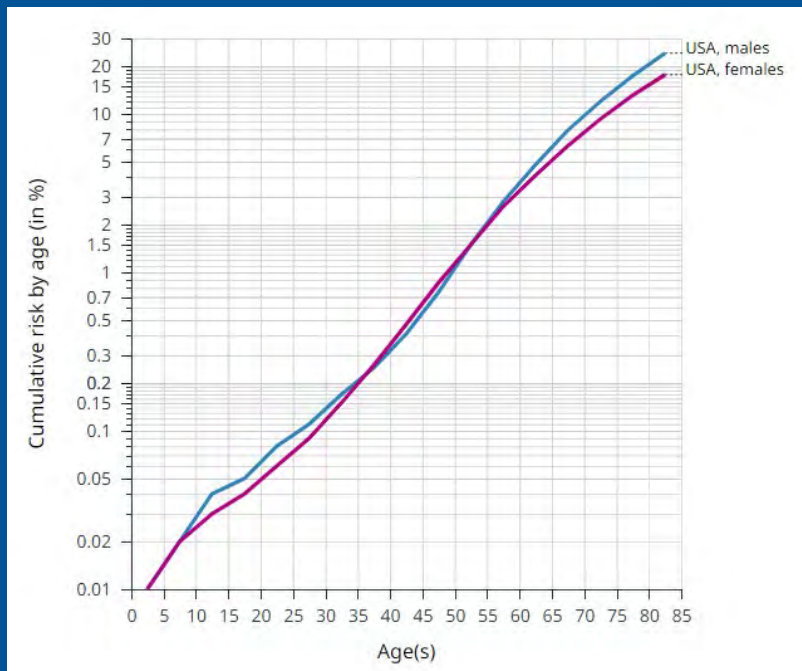
34.2%

Most common cancer cases (2018)



*Source: World Health Organization (WHO), Global Cancer Observatory, 2022.

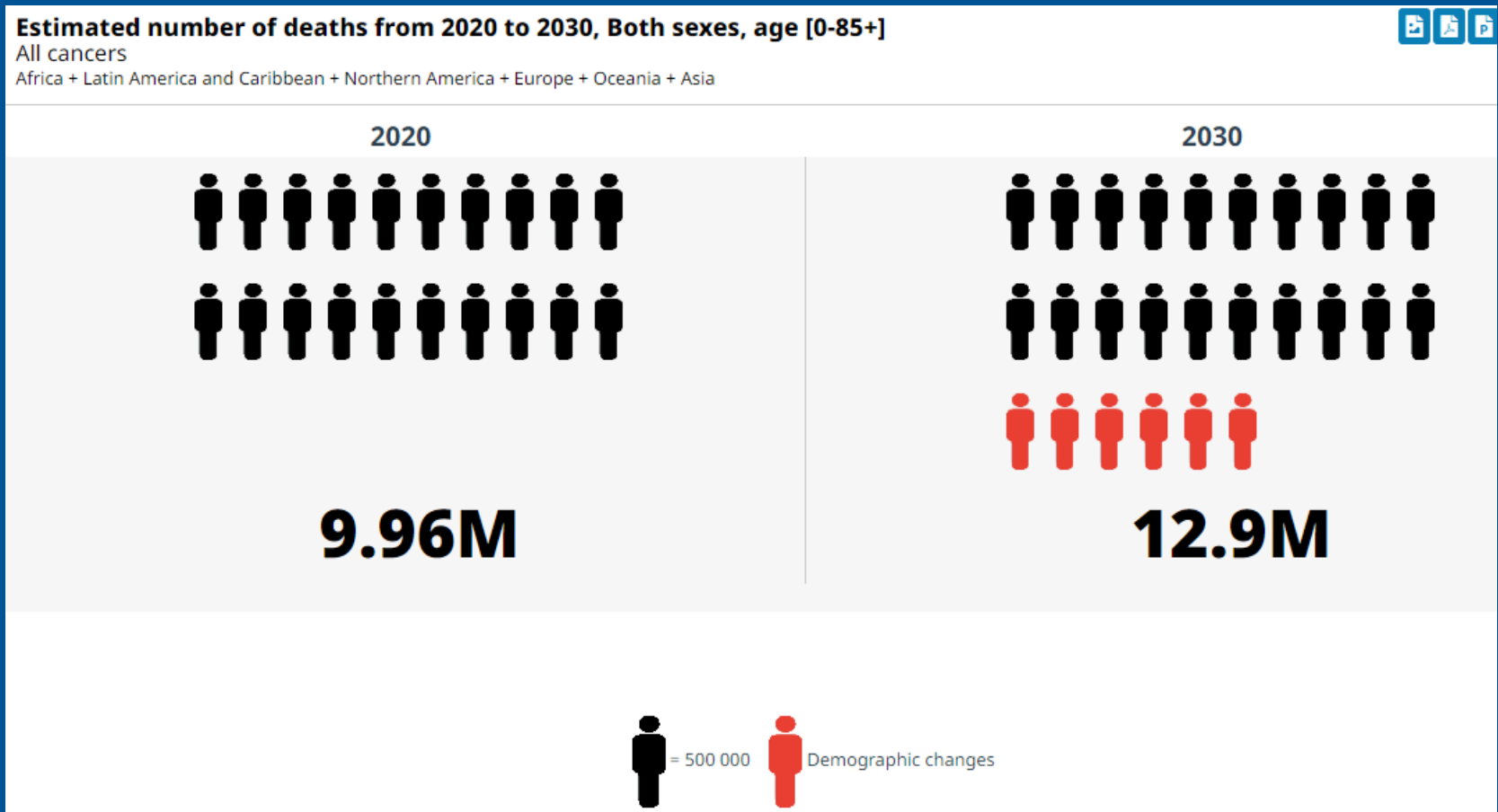
Global Scope of Cancer (Cont.)



*Source: World Health Organization (WHO), Global Cancer Observatory, 2022.

Global Scope of Cancer (Cont.)

Estimated Global Cancer Deaths from 2020 to 2030

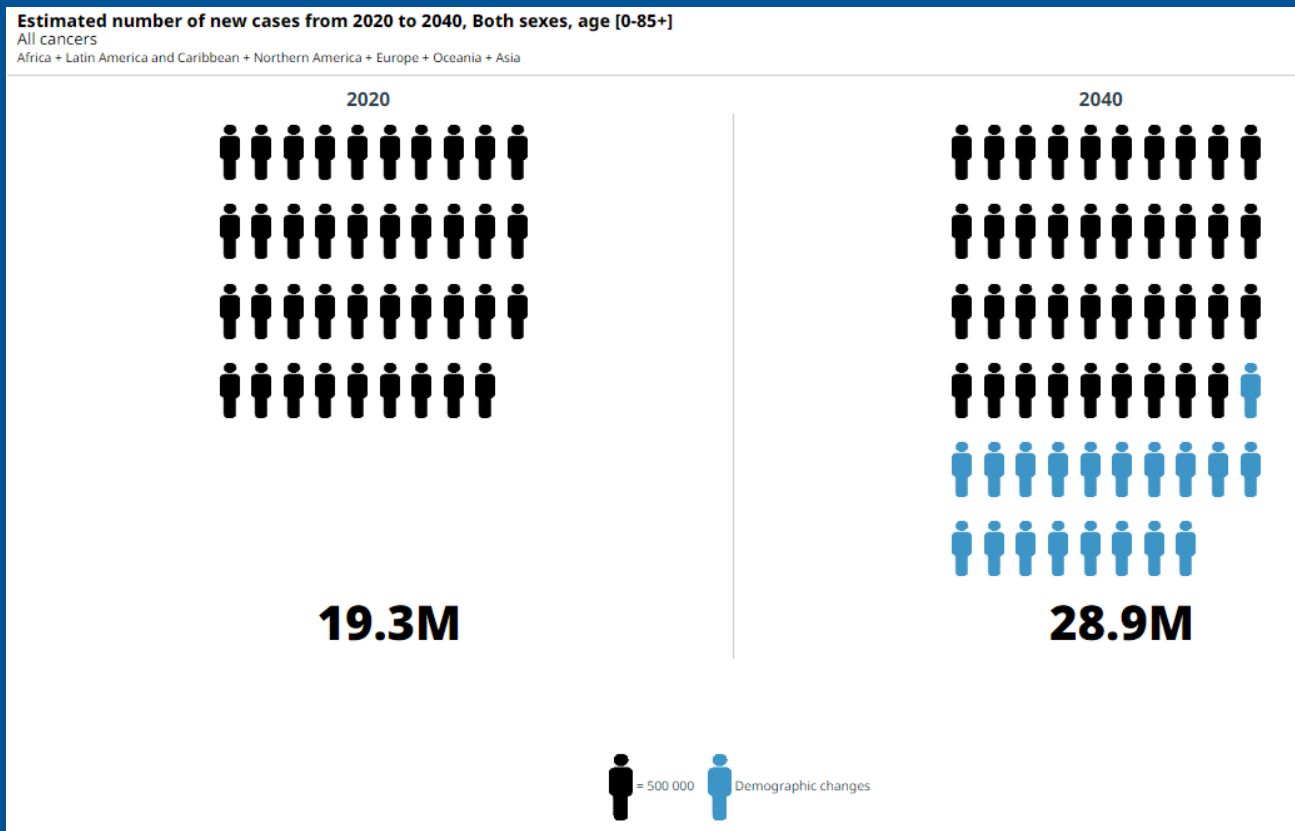


*Source: World Health Organization (WHO), Global Cancer Observatory, 2022.

Global Scope of Cancer (Cont.)



Future Trends in Cancer Incidence with an Aging Population



*Source: World Health Organization (WHO), Global Cancer Observatory, 2022.

Global Scope of Cancer (Cont.)

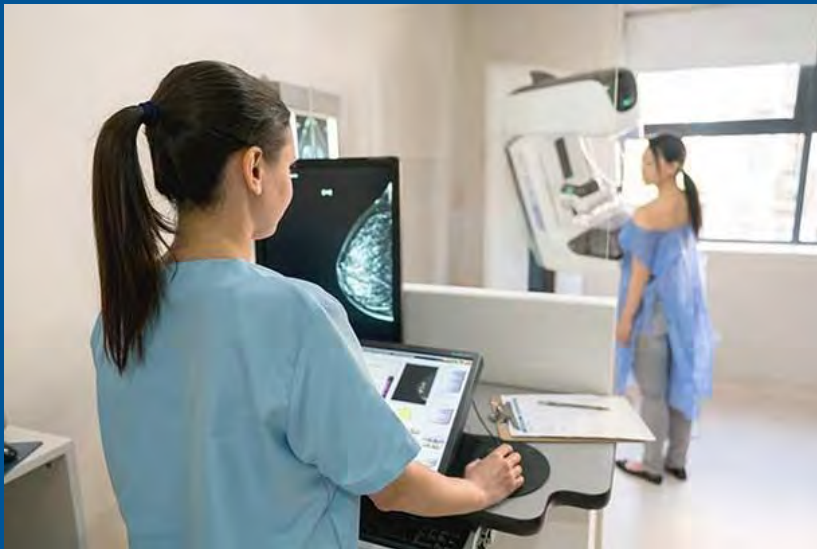
Costs of cancer are also significant. In 2019 alone, costs of cancer care in the U.S. was more than \$21 Billion (NIH SEER Database, 2022).

Although new therapeutic drugs show promise for treating cancer, the costs can sometimes be prohibitive.



In many cases, cancer may be preventable or even detected early with proper screening

Importance of living a healthy lifestyle, and staying up-to-date on age-appropriate cancer screening is KEY.



If you remember wearing these:



REMEMBER THIS?



you probably need a colonoscopy.

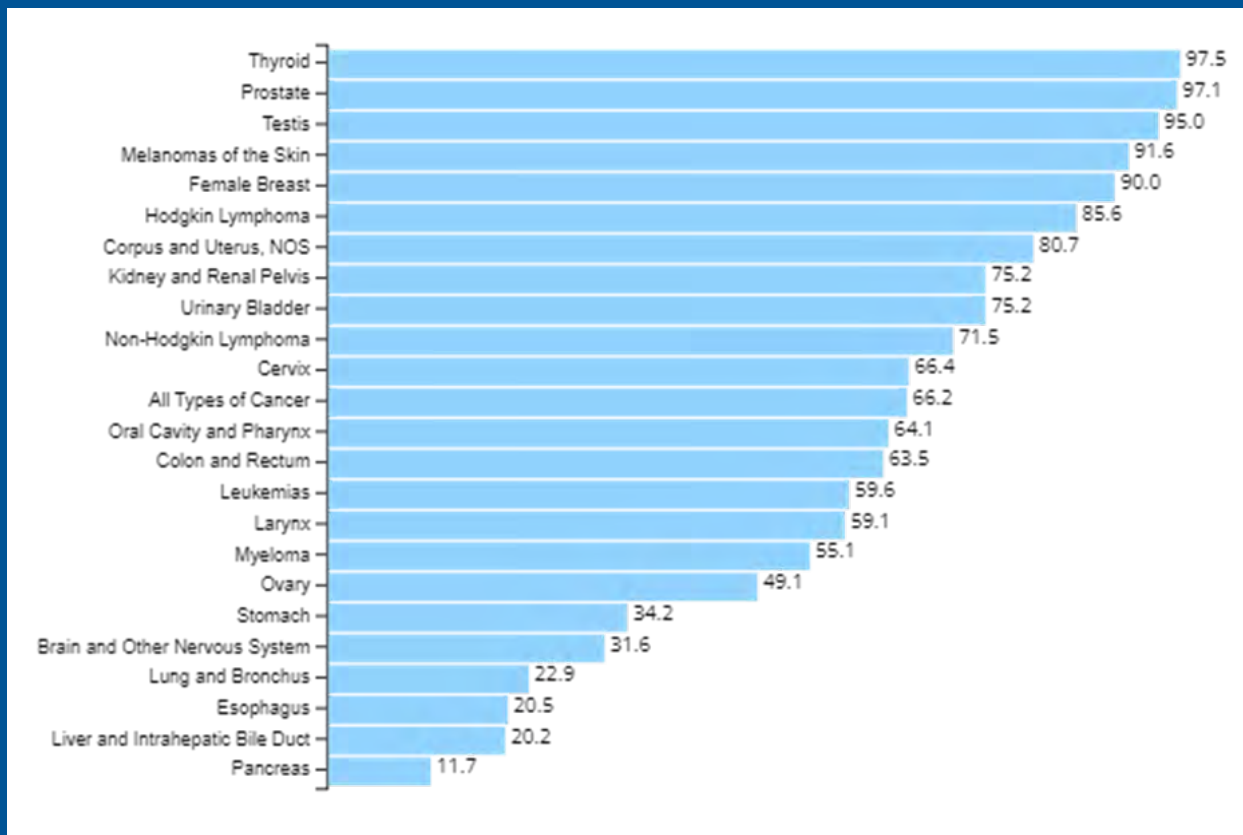


**IF YOU HAD THESE BANGS
THEN IT'S PROBABLY
TIME FOR A
COLONOSCOPY**



Global Scope of Cancer (Cont.)

U.S. 5-Year Overall Survival by Cancer Type & Population



*Source: Centers for Disease Control & Prevention (CDC), 2022

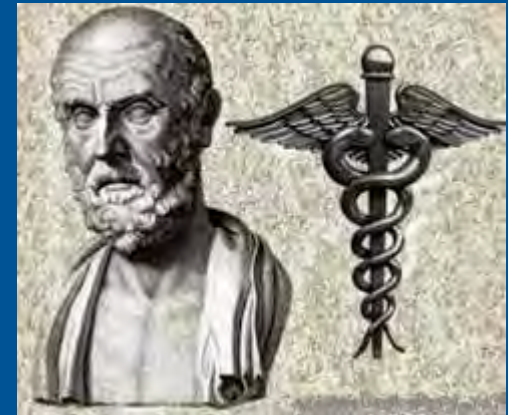
But first, a bit of History...



First writings on cancer was an Egyptian physician, Imotep 2625 BC



Greek historian, Herodotus, describes in story of Atossa breast cancer, 440 BC.



Father of medicine, Hippocrates, first described cancer with word *karkinos* (Greek for “crab”) and for Oncology, *Onkos* (Greek for mass, load or burden), 400 BC.



Claudius Galen,
Greek physician
advocated humoral
theory (red, white,
yellow, & black bile)
“Of black bile without
boiling cometh
cancer.” 160 AD



Andreas Vesalius,
Galenic scholar
and historic
anatomist,
dismissed “black
bile” theory. 1533
AD.

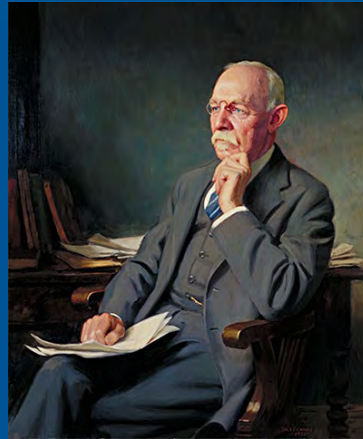


Matthew Ballie, British
anatomist furthered
work of Vesalius, but
described and
illustrated various
tumors and cancers in
great detail. 1793 AD

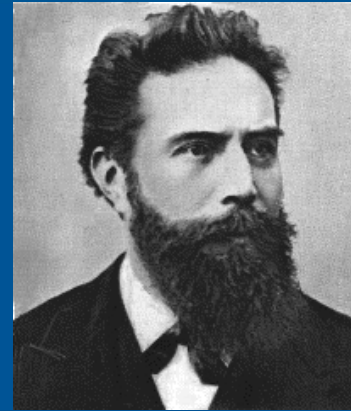
History (Cont.)



John Hunter, a Scottish surgeon, one of the first to begin removing tumors surgically in London, 1760



William Halsted, a New York surgeon who perfected and performed many radical surgeries for cancer (“radical mastectomy”), 1870s



Wilhelm Röntgen, a German scientist who discovered X-rays as a way to look beyond the skin



Marie Curie worked with fellow scientist Pierre in Paris to further work on radioactivity with discovery of radium (basis for radiotherapy)

WINNER OF THE PULITZER PRIZE

THE
EMPEROR
OF ALL
MALADIES



A BIOGRAPHY OF CANCER

SIDDHARTHA
MUKHERJEE

'A tale of hopes, dreams and pincer-sharp disappointment.
Cancer has a master storyteller' *INDEPENDENT*

Cancer usually requires a multidisciplinary approach, and may involve surgery (surgical oncology), radiotherapy (radiation oncology), or systemic therapy (medical oncology). **There are often many options for treating cancer, with some overlap in treatments.**

Types of Systemic Cancer Treatments (In Brief):

- Cytotoxic chemotherapy
- Hormonal or endocrine therapy
- Molecularly targeted therapy
- Hematopoietic stem cell transplant
- Miscellaneous or Unique Agents
- Immunotherapy

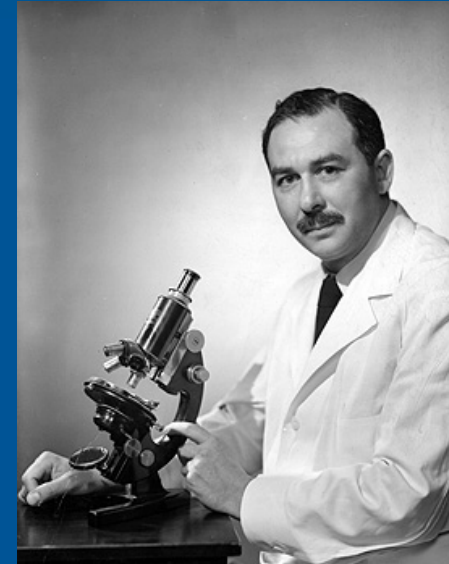


Traditional Chemotherapy: A Brief History

One of the **key pioneers and fathers of modern chemotherapy** was **Dr. Sidney Farber**

He was a pathologist who studied pediatric acute leukemia in Boston in the 1940s and founded a Children's Cancer Research Foundation, and developed many clinical research trials for cancer.

Dr. Farber **helped describe how leukemia cells proliferate or die**, and he developed chemotherapy treatments for Acute Lymphoblastic Leukemia (ALL)



Traditional Chemotherapy: A Brief History (Cont.)

- Dr. Farber promoted use of **multi-agent chemotherapy**, which had improved effect on treating the cancer and had resulted in some cures
- **Chemotherapy is considered “cytotoxic”** (toxic to cells, including cancer cells)
- It **also affects the body’s normal cells**, and this is what leads to the side-effects
- Throughout the 20th Century, **many discoveries on the science of cancer, pharmaceuticals, and the concept of environmental carcinogens** (e.g., smoke, soot, radiation exposure, chemicals, gases, poisons, etc.), which in turn fueled the development of new chemotherapy approaches





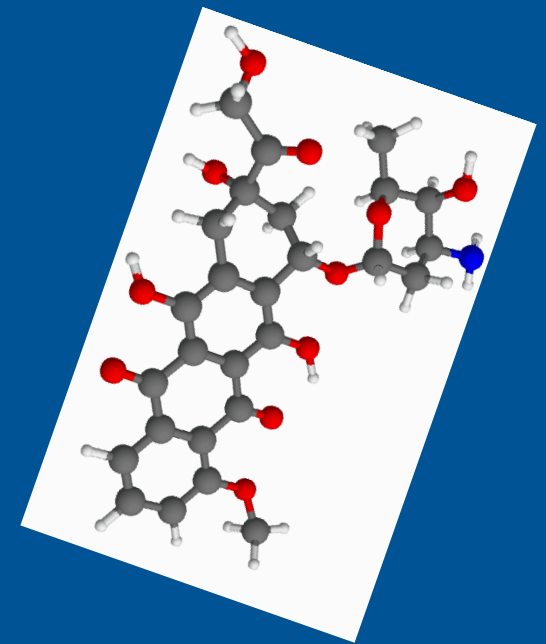
*Source: Google Images WWI Nitrogen Gas

Types & Classes of Chemotherapy:

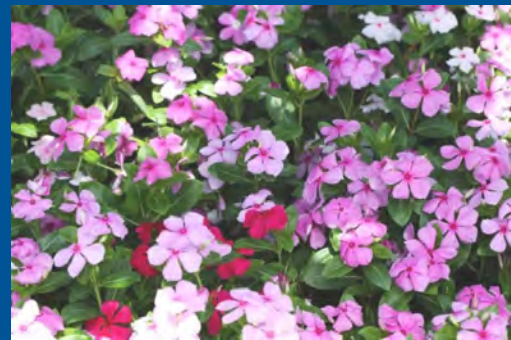
- **Alkylating Agents** (Historical relevance of WWI & Mustard Gas, 1914)
 - Examples: Bendamustine, Cyclophosphamide, & Temozolamide
- **Anti-Metabolites** (1940s, Use of Aminopterin by Dr. Sidney Farber)
 - Examples: Methotrexate, Pemetrexed, Cytarabine, & Gemcitabine
- **Platinum Based Agents** (1960s, discovered by Dr. Barnett Rosenberg)
 - Examples: Cisplatin, Carboplatin, & Oxaliplatin

Types & Classes of Chemotherapy (Cont.):

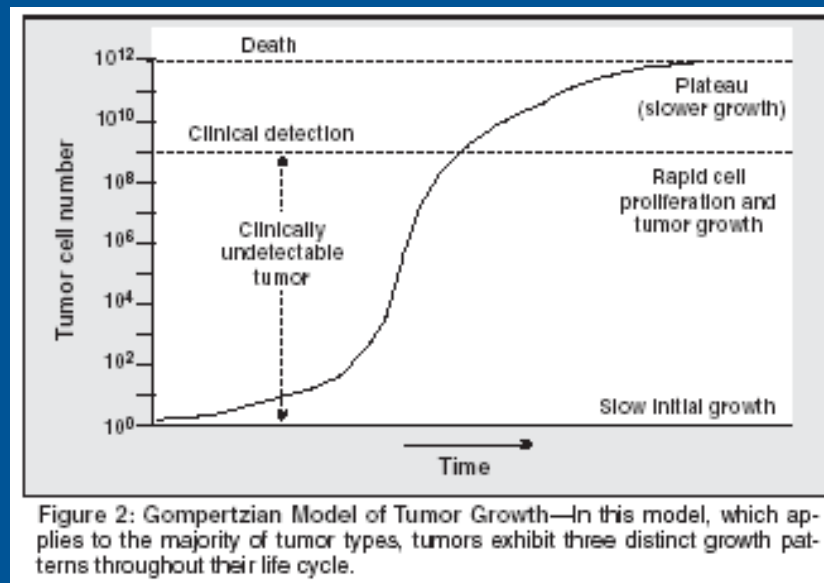
- **Topoisomerase Inhibitors** (1960s, derived from plants & bacteria)
 - Examples: Anthracyclines (Doxorubicin, Daunorubicin, Idarubicin) & Camptothecins (Irinotecan, Topotecan)
- **Anti-Tubule Agents** (1950s, derived from leaves of the periwinkle plant & 1960s, derived from coniferous Yew tree, *Taxus brevifolia*)
 - Examples: Taxanes (Paclitaxel, Docetaxel) & Vinca Alkaloids (Vincristine, Vinblastine)



Traditional Chemotherapy (Cont.)



Model of tumor cell growth over time



***Source:** Cancer Network, Hudis, C.A., 2005, Clinical Implications of Antiangiogenic Therapies *Oncology* 19(4;3)

Model of tumor cell death (logarithmic) from cytotoxic chemotherapy cycles over time

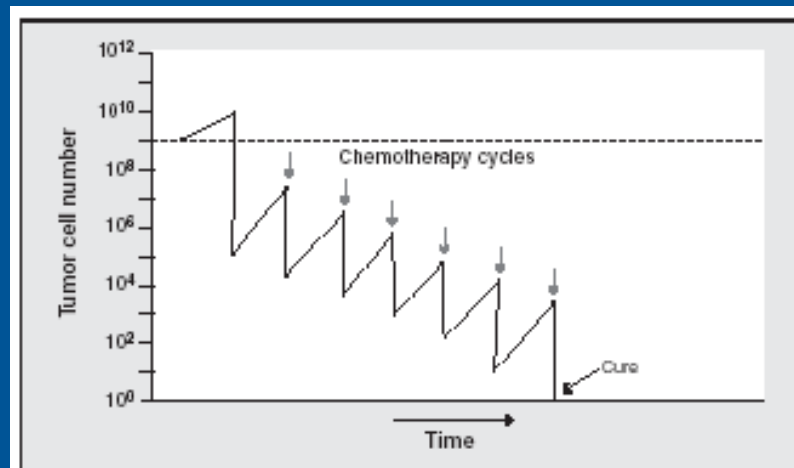
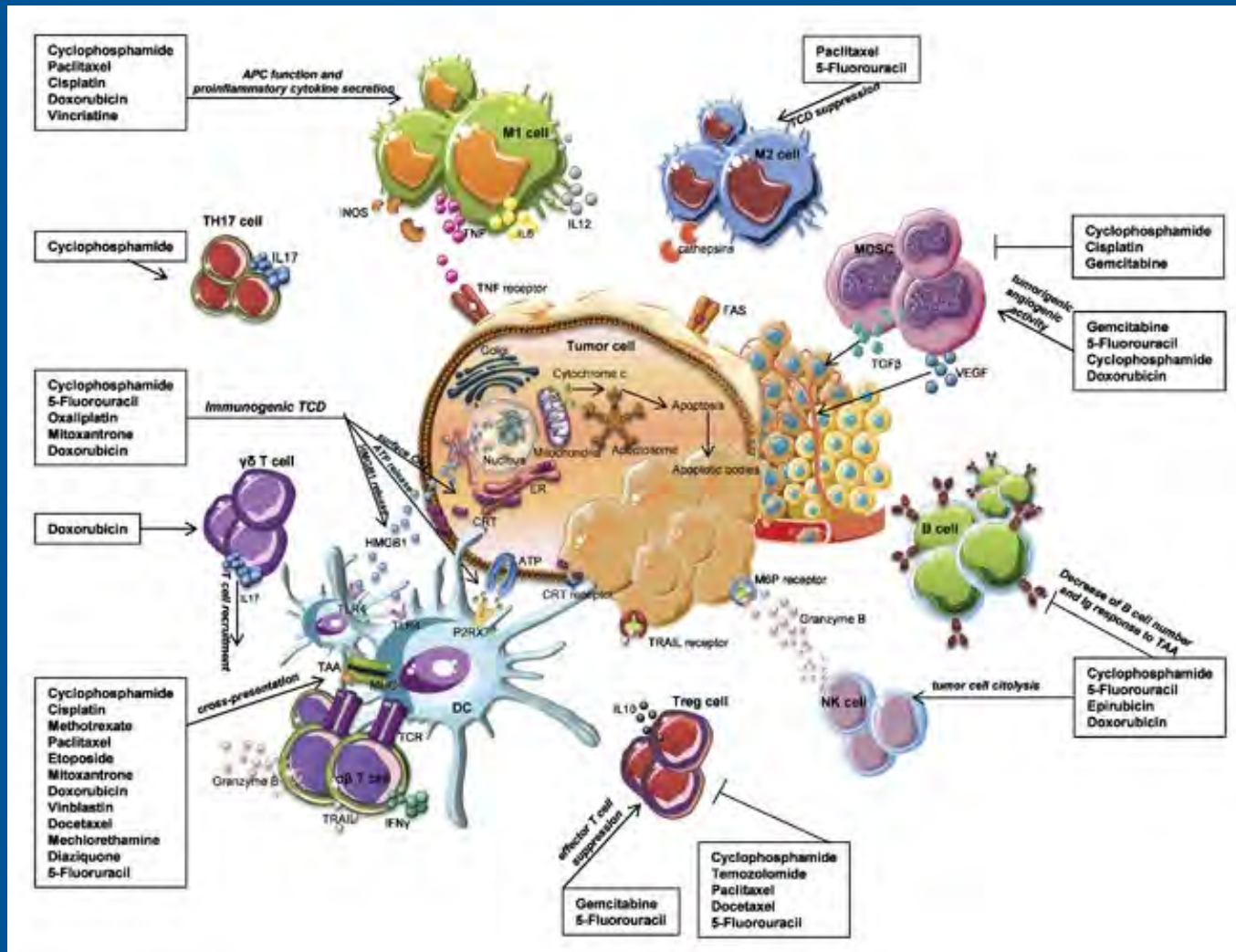


Figure 1: Log-Kill Kinetics—In a log-kill kinetics model, if a given dose of chemotherapy reduces tumor burden from 10^9 to 10^5 , the same dose would reduce the burden from 10^4 to 10^0 .

***Source:** Cancer Network, Hudis, C.A., 2005, Clinical Implications of Antiangiogenic Therapies *Oncology* 19(4;3)

Traditional Chemotherapy (Cont.)



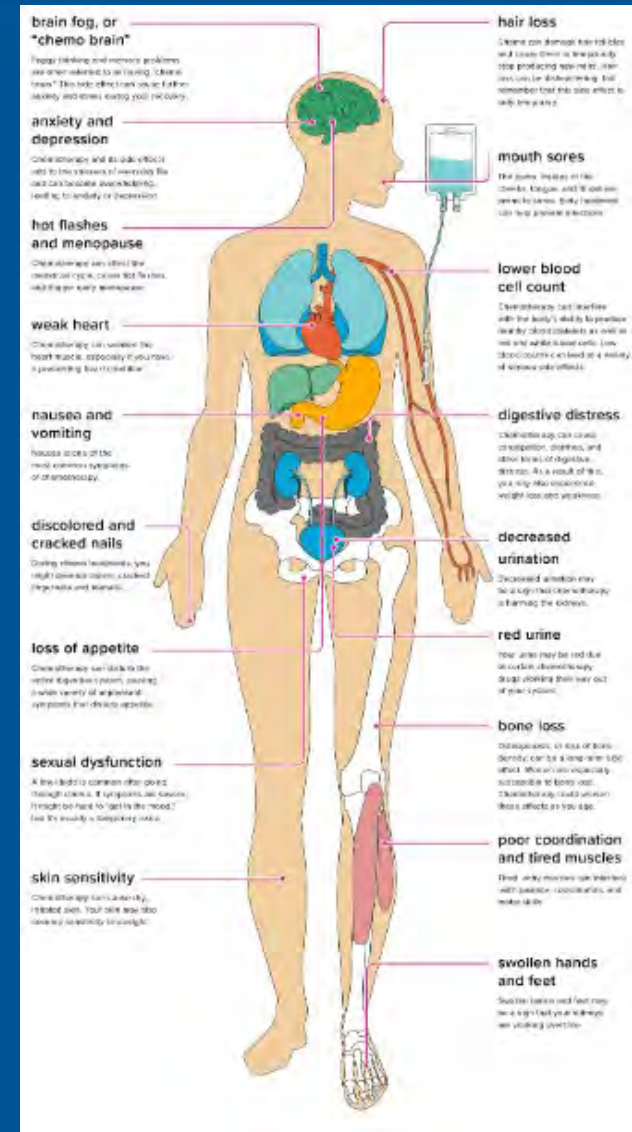
*Source: Google Images on Cytotoxic Chemotherapy

Traditional Chemotherapy (Cont.)

Despite the benefits and effectiveness of chemotherapy for many cancers, the side-effects of chemotherapy can be significant and sometimes debilitating



*Source: Google Images on Cytotoxic Chemotherapy

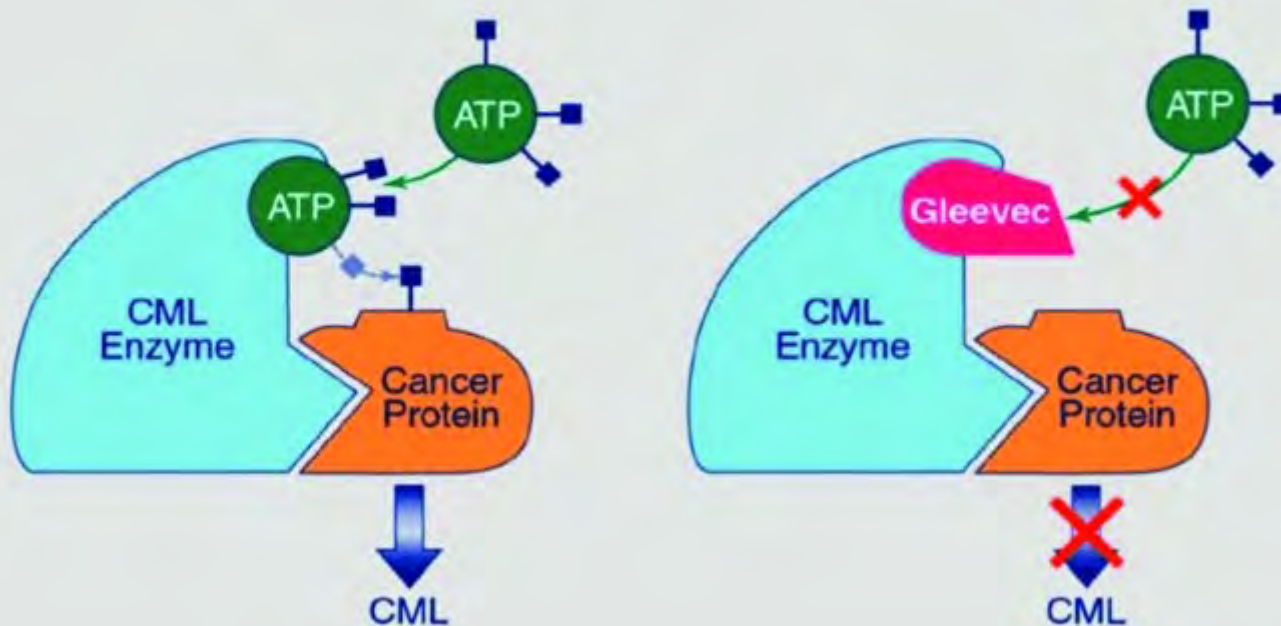


Molecularly Targeted Agents & Monoclonal Antibodies

- These drugs bind to or interact with proteins specific to the cancer, such as “kinases” and “proteases”
- Importance of oncogenes & molecular “signatures” of the tumor
 - Key Example: Imatinib (Discovered in 2001, inhibits BCR-ABL in Chronic Myeloid Leukemia or CML)
 - Other Examples: Erlotinib & Cetuximab (EGFR), Crizotinib (ALK), Trastuzumab (HER2), Bevacizumab & Axitinib (VEGF), Regorafenib (RAF), Dabrafenib (BRAF), Everolimus (mTOR inhib.), Vorinostat (HDAC inhibitor), Ibrutinib (BTKI), Bortezomib (protease inhib.), & Rituximab (anti-CD20 mAb)

Imatinib (Gleevec) Mechanism of Action for CML

Gleevec: HOW IT WORKS



*Source: Google Images for Imatinib Mechanism of Action

Hormonal or Endocrine Therapies

- Used to treat hormonally responsive types of cancer such as certain breast cancers, prostate cancer, or uterine cancer (among others)
 - Examples: Tamoxifen (SERM), Anastrozole (A.I.), Fulvestrant, Leuprolide (LH-RH, Anti-Androgen), Bicalutamide (Anti-Androgen), Enzalutamide (Anti-Androgen), Abiraterone (CYP Androgen Inhib.), & Octreotide

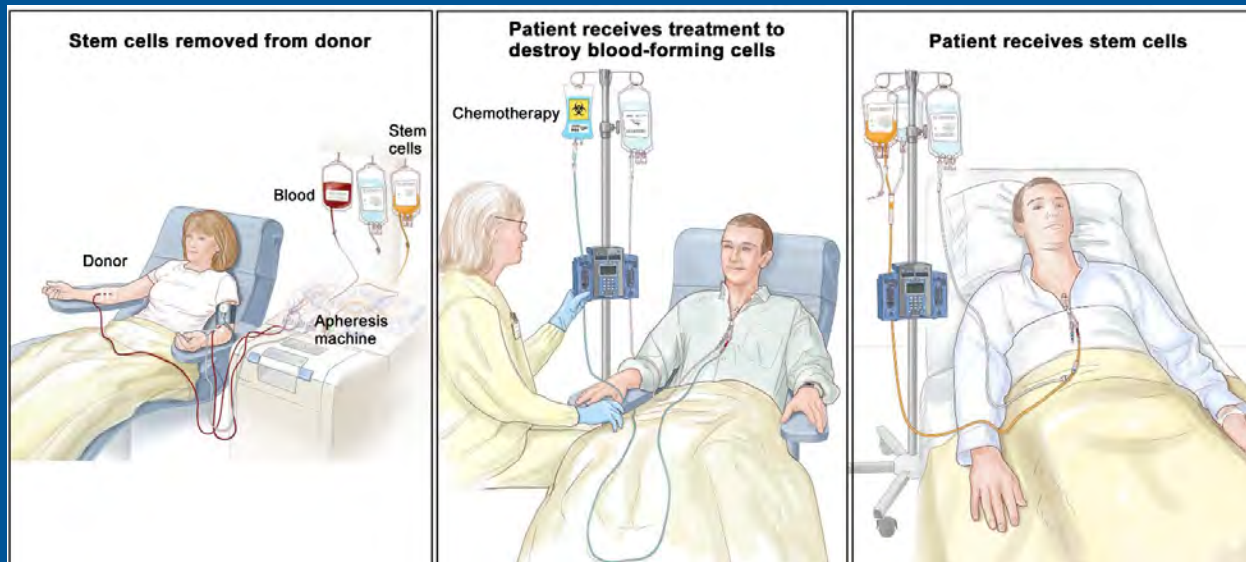


*Source: Google Images for Lupron & Tamoxifen

Other Types of Cancer Systemic Therapies (Cont.)

Hematopoietic Stem Cell Transplant (a.k.a., Bone Marrow Transplant)

- Used mainly for certain types of hematologic malignancies such as Acute Myeloid Leukemia (AML) or Non-Hodgkin Lymphomas (NHL)
- **Includes two main types:** Allogeneic (donor cells) and Autologous (patient's cells)



*Source: Google Images & NIH for Stem Cell Transplant

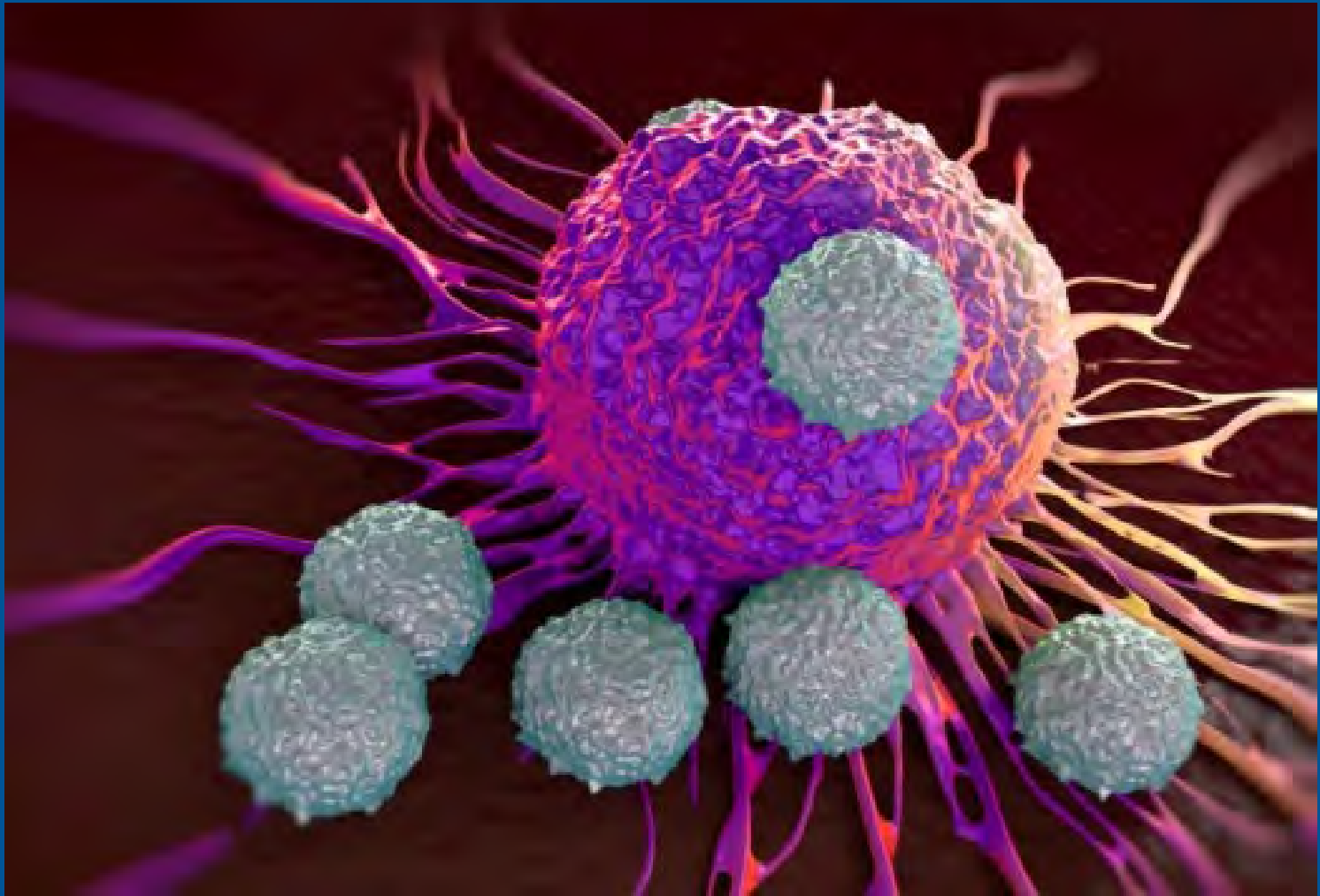
Miscellaneous Chemotherapeutics & Unique Agents:

- **Epigenetic Modification & Hypomethylating Agents** used in Myelodysplastic Syndrome or MDS & AML)
 - Examples: Azacitidine, Decitabine
- **Immunomodulating Agents (a.k.a., Imids)** used in cancers like Multiple Myeloma
 - Examples: Lenolidomide, Pomalidomide
- **Anti-tumor Antibiotics**
 - Example: Bleomycin
- **Enzymes (proteins)**
 - Example: L-Asparaginase

Miscellaneous Chemotherapeutics & Unique Agents (Cont):

- **Non-classic Antimetabolites**
 - Example: Procarbazine
- **Antibody-Drug Conjugates**
 - Example: Ado-trastuzumab emtansine (Kadcyla)
- **Anti-tumor Vaccines & Vaccines that Prevent Virus-Mediated Cancer**
 - Example: The Human Papilloma Virus (HPV) Vaccination (Can prevent Cervical Cancer and Certain Head & Neck Cancers)
- **Gene Therapy**
 - Programming genetic information in cells to change a disease process, such as in Thalassemia and new applications in immunotherapy

IMMUNOTHERAPY





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Every cancer is different, every person's biology and specific clinical situation is different, and there may be many factors that determine whether a patient is a good candidate (or not) for consideration of immunotherapy.

An in-depth discussion of the individual benefits or risks of immunotherapy, the specific indications (supported by national guidelines and evidence for each type and stage of cancer), and any contraindications or significant side-effects or complications related to the use of immunotherapy (or any related systemic cancer therapies) is beyond the scope of this lecture and is best reviewed in private consultation with a patient's personal qualified oncologic specialist.

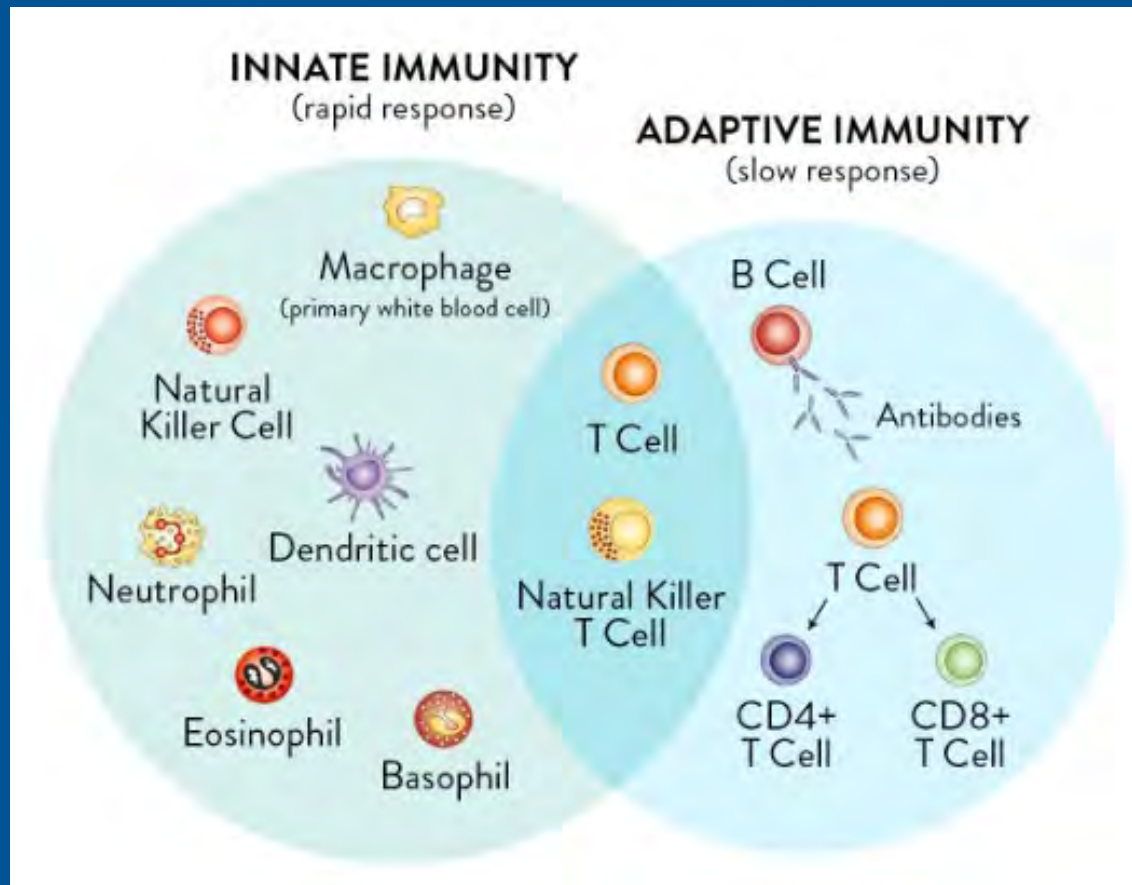
Innate Immunity:

- Rapid onset; present since birth
- Physical barriers (junctions between cells, mucous and blood vessel membranes)
- Antimicrobial peptides (AMPs) on surface of cells
- Inflammatory-related serum proteins & cytokines
- Phagocytes: Neutrophils, Monocytes, & Macrophages

Adaptive (Humoral & Cellular) Immunity:

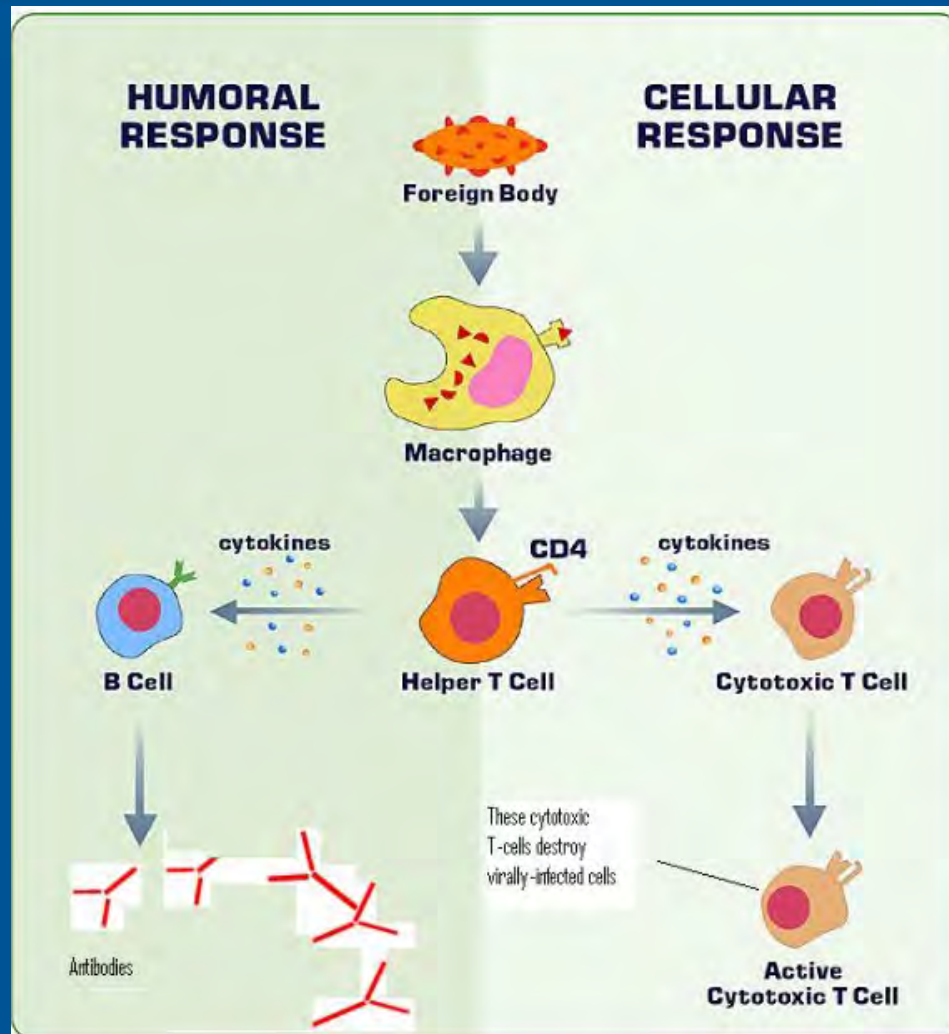
- Passive (fetal development)
- Active (after birth); slower
- Antigen stimulation results in activation and signaling for B-Cell & T-Cells (lymphocytes)
- Plasma Cells & Memory B-Cells produce antibodies
- Complement system

The Immune System (Cont.)



*Source: Google Images for immune & lymphatic system

The Immune System (Cont.)



*Source: Google Images for immune & lymphatic system

The Immune System (Cont.)

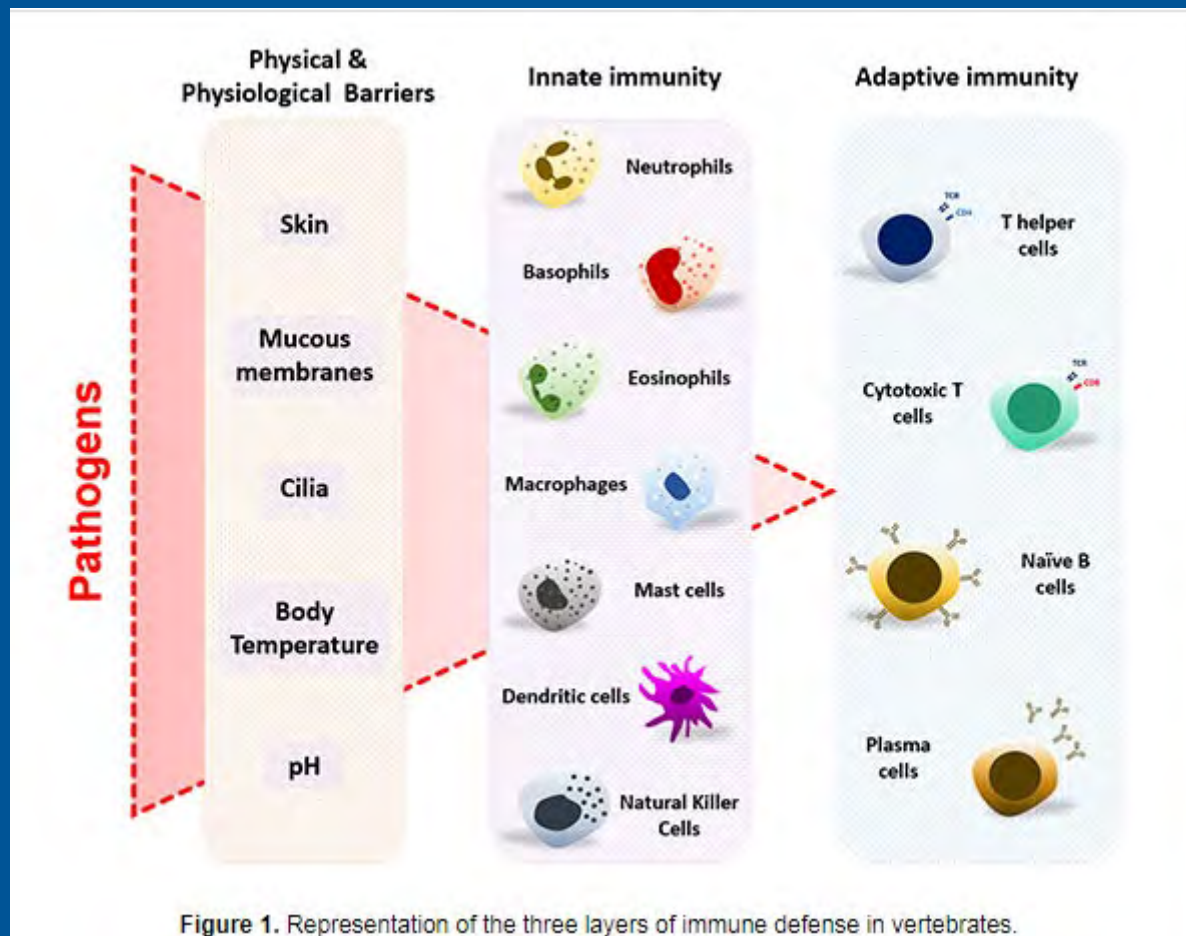
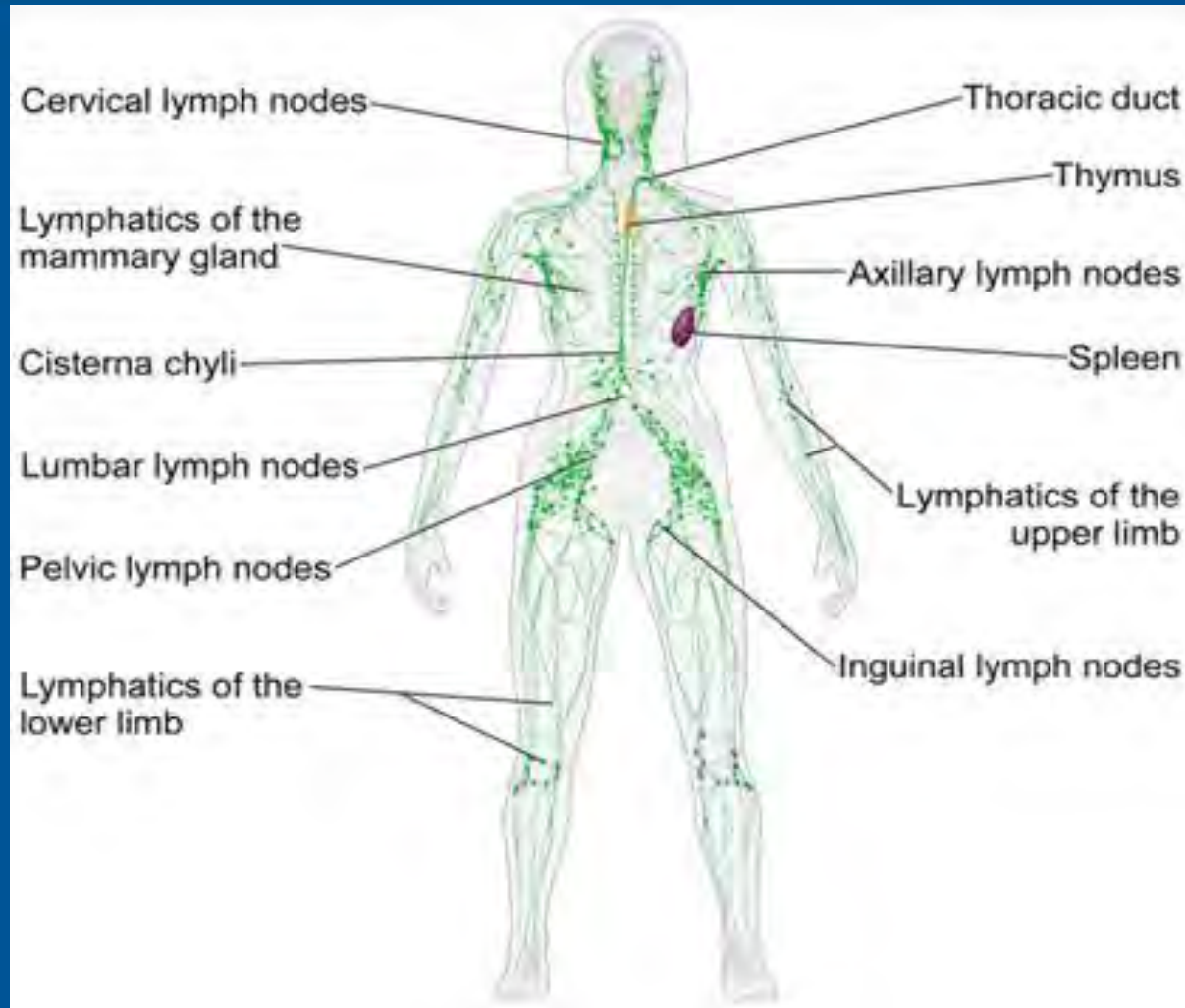


Figure 1. Representation of the three layers of immune defense in vertebrates.

*Source: Google Images for immune & lymphatic system

The Lymphatic System (Related to Immunity)

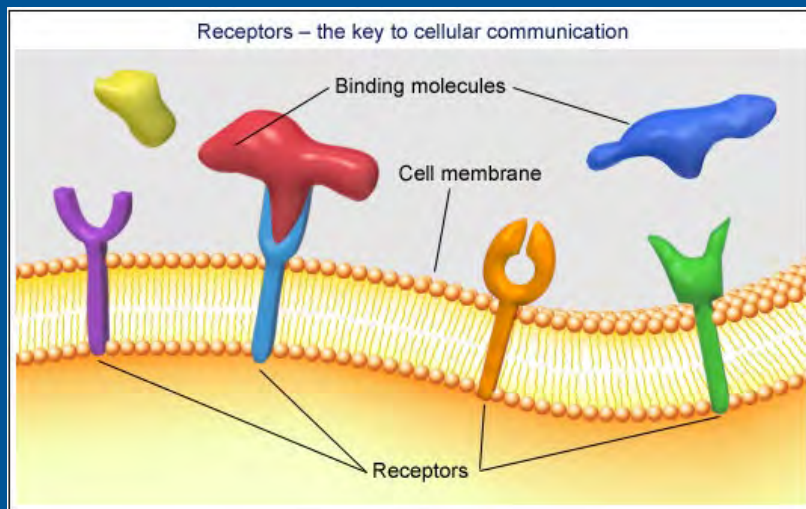
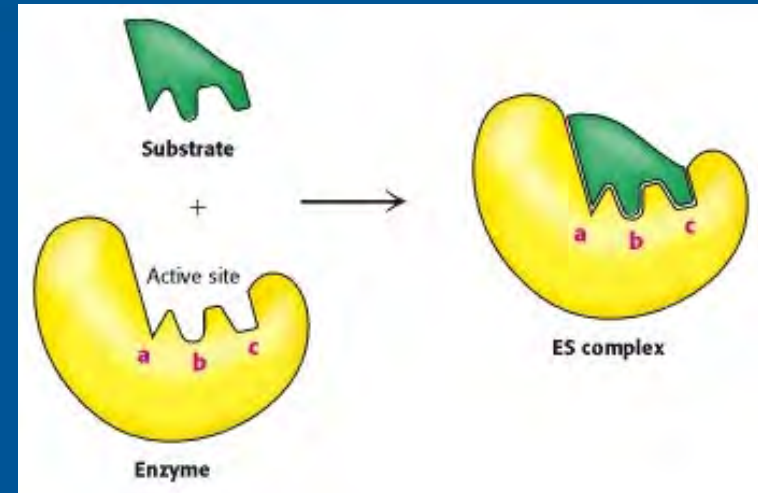
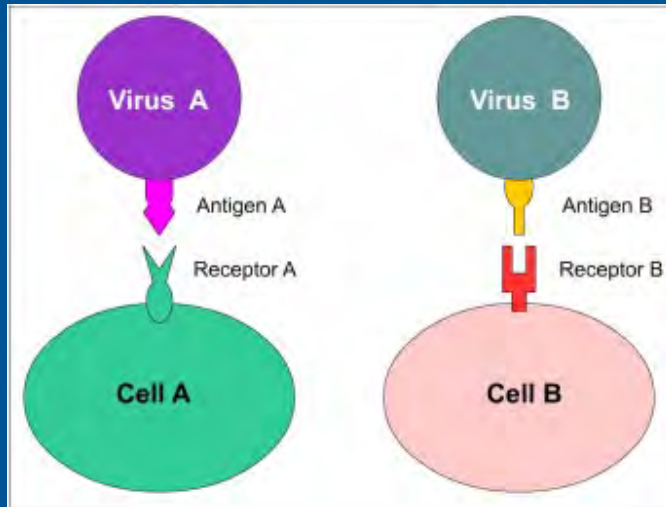


*Source: Google Images for immune & lymphatic system

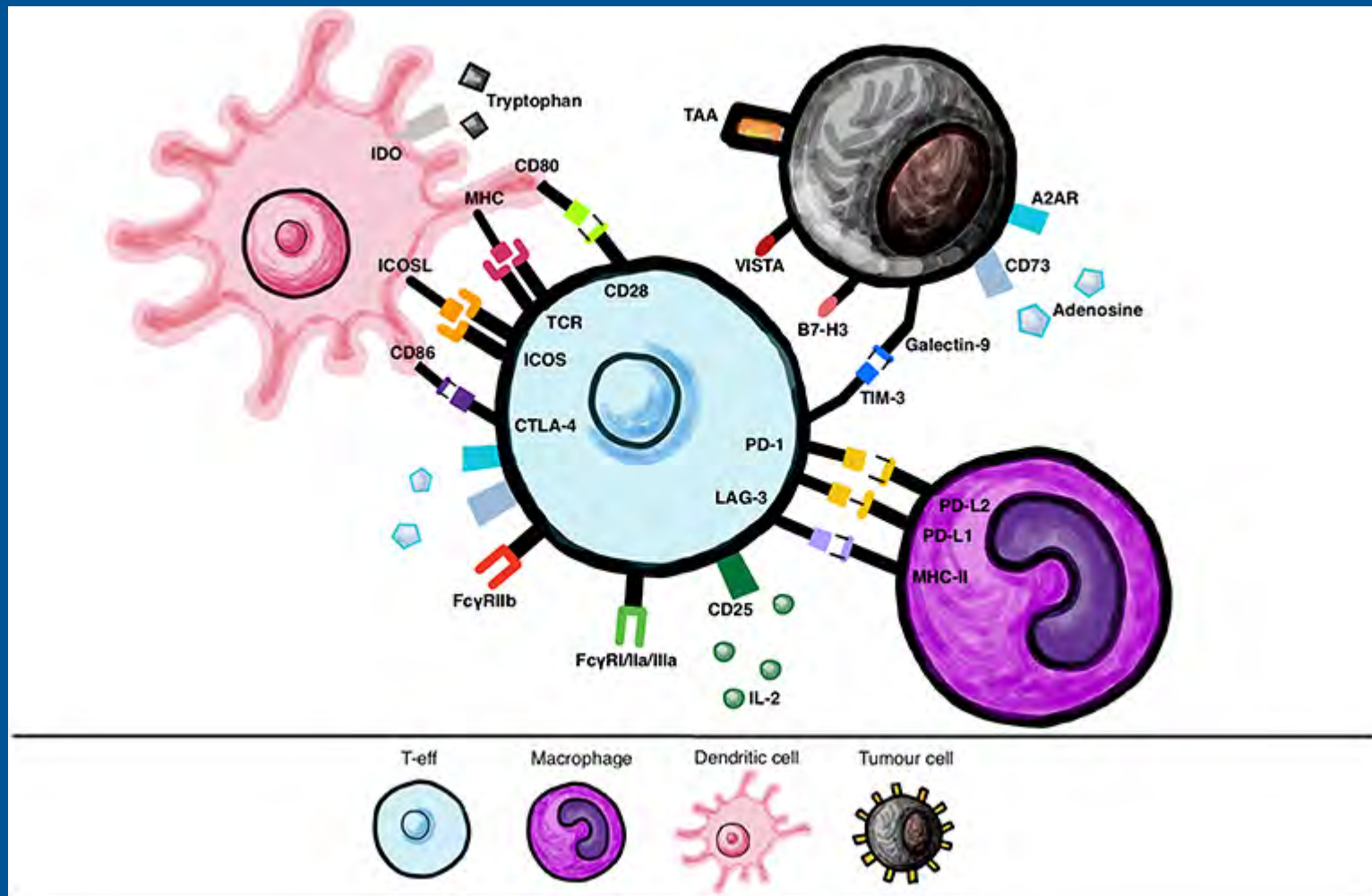
Immune System: “Lock & Key” Concept

- Useful to think about the immune system cells and molecular interactions like a **“lock and key”**
- **Cells have MANY proteins** (a.k.a. receptors) on their surface that function as **“locks” or “keys”** and lead to various reactions within the body (whether good or bad)
- **Antibodies can be thought of as “keys”** that can recognize and “unlock” a process or block another “key” from using the **“locks.”** They also work this way to target foreign invading proteins (a.k.a. antigen) that can cause illness or infection, engaging them and tagging them for destruction by the body
- In a very simplistic sense, **many pharmaceutical drugs act in the same way** in how they interact with our cells
- **Immunotherapy works similarly to engage cancer cells on a tumor**, and then helps enhance our body’s cell response to help naturally fight cancer and keep it in check

Immune System: “Lock & Key” Concept (Cont.)

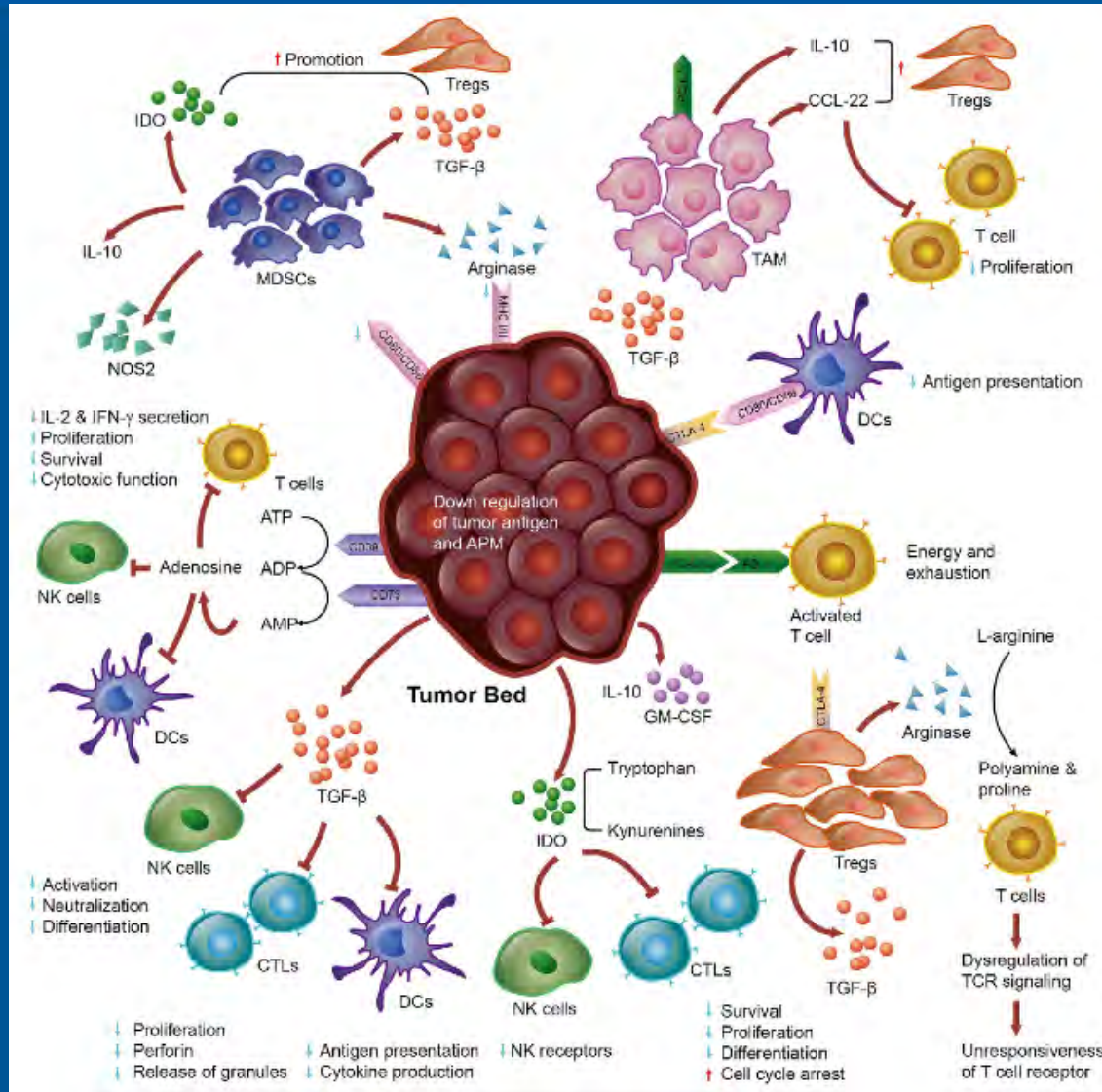


Cellular Interactions: Many Locks & Keys!



*Source: Google Images for immune & lymphatic system

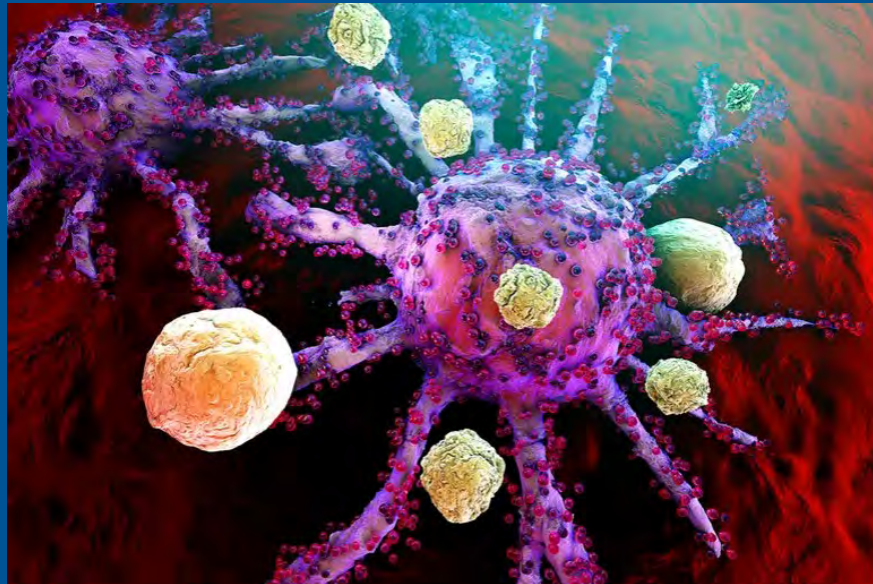
Cellular Interactions: Tumor Microenvironment



*Source: Google Images for immune & lymphatic system

The Immune System (Cont.)

- The immune system also **plays a major role in regulation of cell growth** (and overgrowth), which **helps to keep cancer in check**.
- This is accomplished through **multiple cellular and regulatory interactions**, including **immune checkpoints** and “**programmed cell death**” (i.e., apoptosis)



*Source: Google Images for immune & lymphatic system

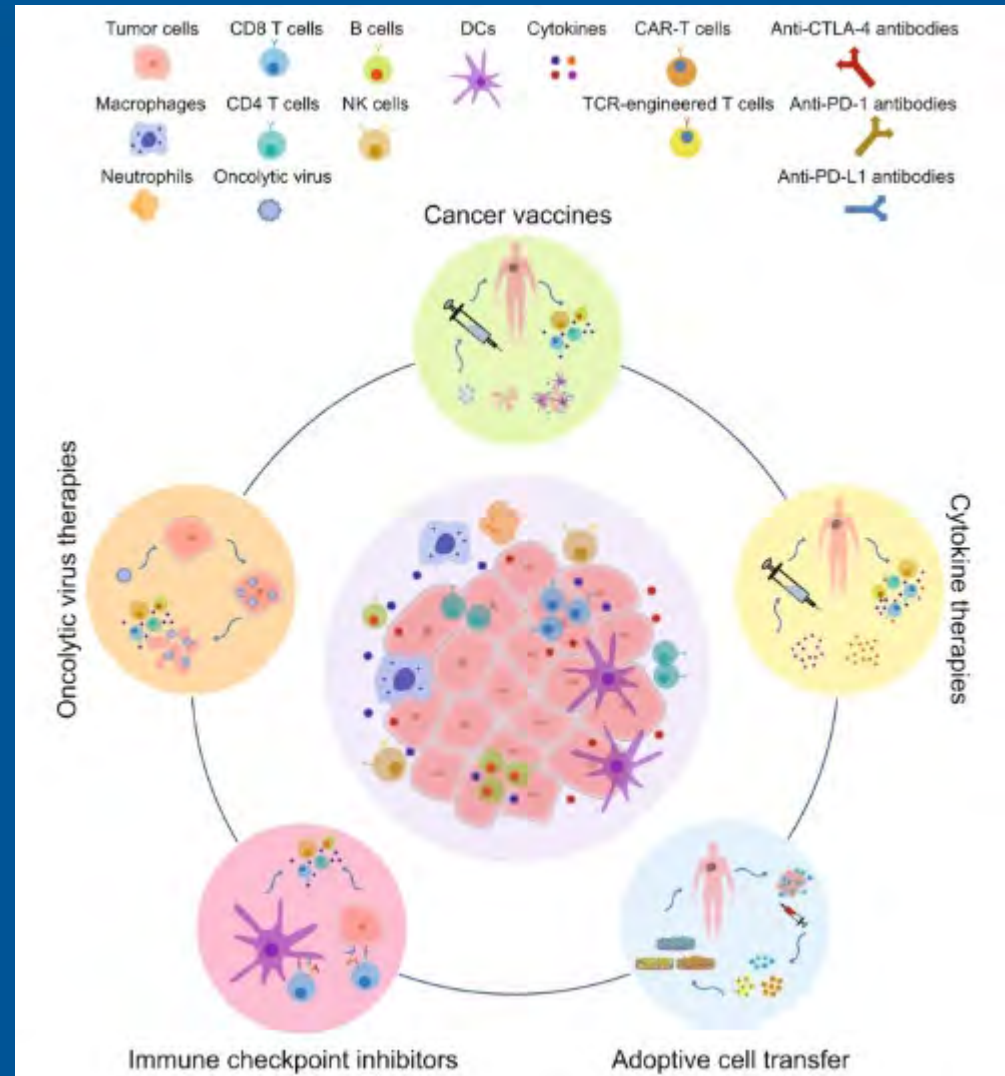
Immunotherapy: What is it? How is it different?



- Many **cancers evolve and develop mechanisms of resistance** to standard treatments.
- One way that cancer grows and progresses is through **evading the body's defenses** and in effect, “turning off” many of the immune system’s surveillance mechanisms
- Immunotherapy offers **a way to harness the body’s natural ability to fight cancer** through reversing the tumor’s evasion tactics
- The intensified immune response and chemical reactions that follow **help to destroy the existing cancer cells and prevent it from growing** or cropping up in new areas
- This **can lead to a durable response, remission, or in some cases even a cure** to certain cancers, and **often with far less toxic side-effects** compared to traditional chemotherapy

Types of Immunotherapy:

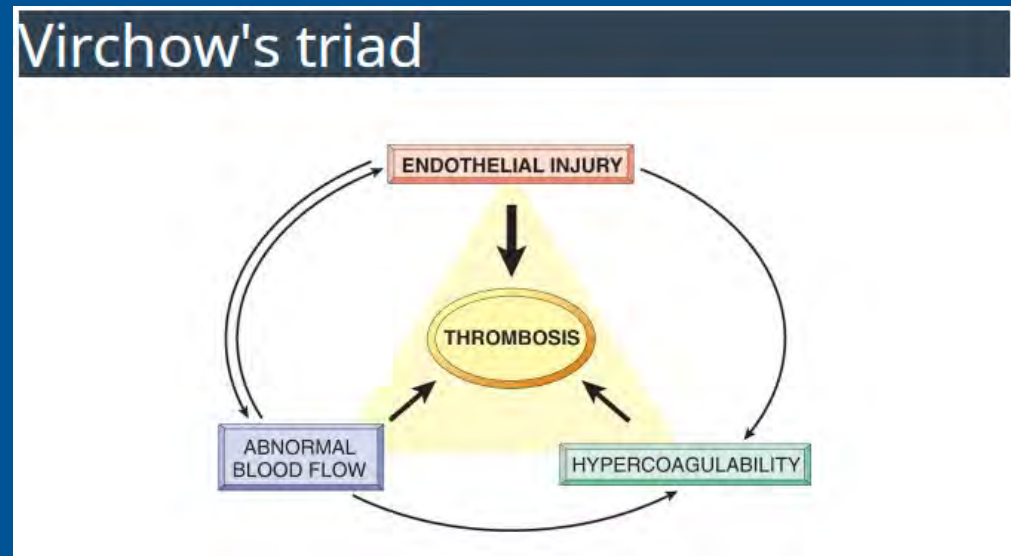
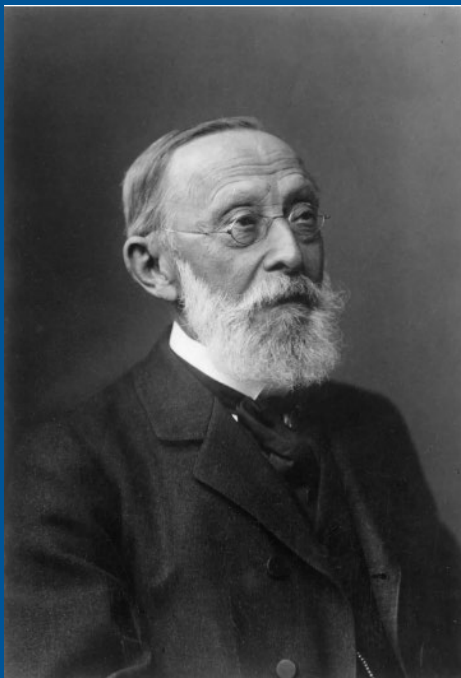
- **Cancer Vaccines & Oncolytic Virus Related Therapies**
- **Cytokine Therapies**
- **Immune Checkpoint Inhibitors**
- **Adoptive Cell Transfer Therapies**



*Source: Google Images Immunotherapy

Immunotherapy: History of Development

Dr. Rudolf Virchow, a German physician in 1800s, was the first to make a connection between inflammation in the body and the immune response when studying blood clots, leading to Virchow's Triad.



*Source: Google Images for Immunotherapy & History

Dr. William Coley (late 1800s / early 1900s) is **considered the father of immunotherapy**. He was the first to study it with regard to bone sarcoma by injecting *Streptococcal pyogenes*, a type of bacteria, into the tumor to stimulate an immune response.



By the 1960s and 1970s, Cytokines were discovered and studied as potential cancer treatments. **Cytokines are chemical messengers that are released during stress, inflammation, infection, or tumorigenesis (cancer formation).**

The key cytokine related therapies included **Interleukin-2 and Interferon Alfa**. These cytokines helped to activate T-Cells to fight the cancer. Most studied in melanoma and chronic myeloid leukemia (CML).



*Source: Google Images for Immunotherapy

Immunotherapy: History of Development (Cont.)

Dr. Steven Rosenberg at the NIH was the first to develop a robust immunotherapy that consisted of surgically removing melanoma tumors and isolating the **“Tumor Infiltrating Lymphocytes” (a.k.a, TILs)**, genetically engineered them to eliminate cancer cells and then re-infused the T-Cells into patients to treat their malignancy (melanoma initially).

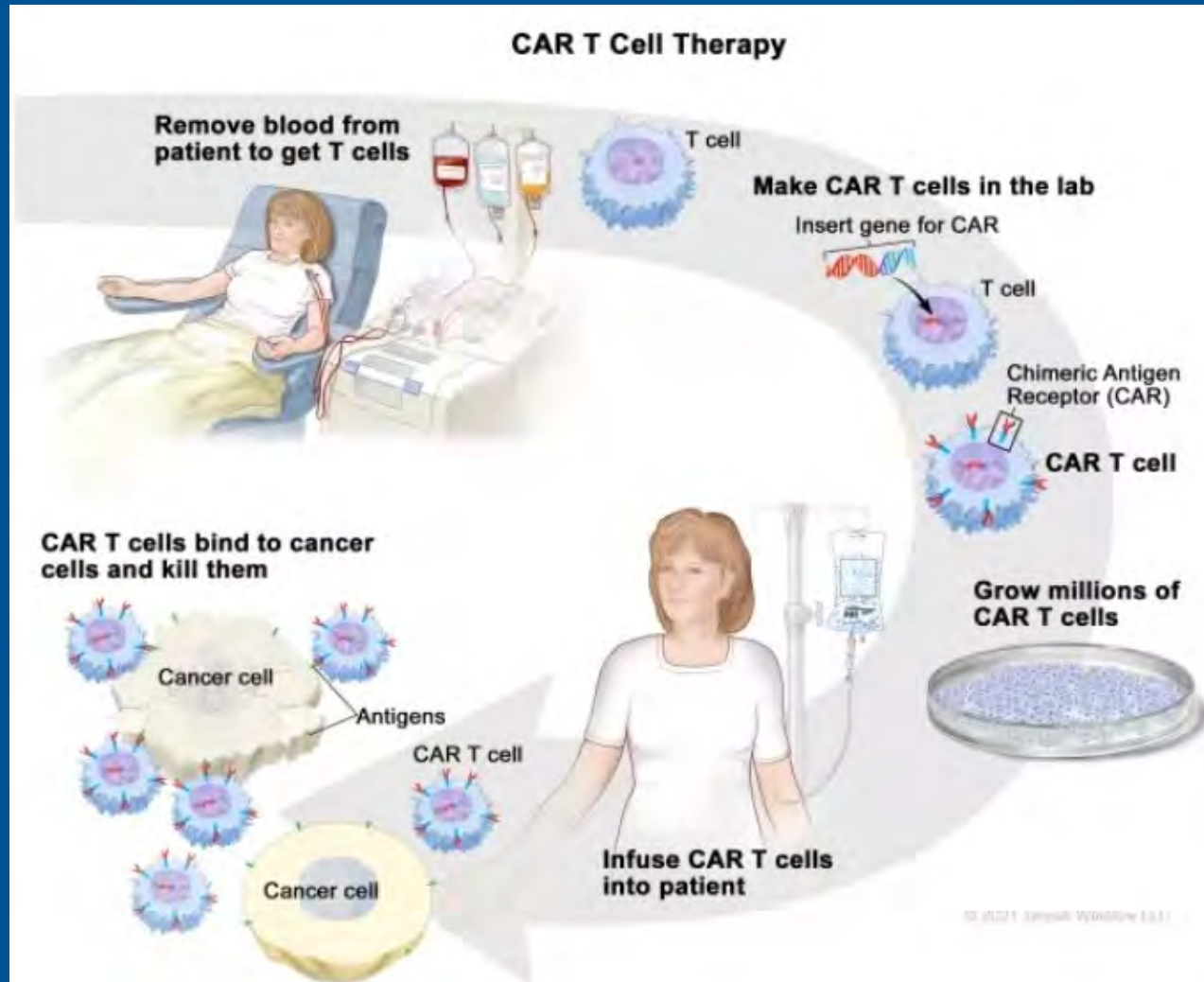
Known as **Adoptive Cell Transfer** or **Adoptive Cell Therapy**

This led to the eventual development of another type of “next generation” cellular based immunotherapy called **Chimeric Antigen Receptor Therapy (a.k.a., CAR-T Cell Therapy)**, with many evolving applications including for Non-Hodgkin B-Cell Lymphomas refractory to other treatments.



*Source: Google Images for Immunotherapy

Immunotherapy: CAR-T Cell Therapy



*Source: Google Images for Immunotherapy

Immunotherapy: History of Development (Cont.)

The greatest impact on cancer immunotherapy thus far has been the type known as **Checkpoint Inhibitors (a.k.a., PD-1 / PD-L1 & CTLA-4 Inhibitors)**.

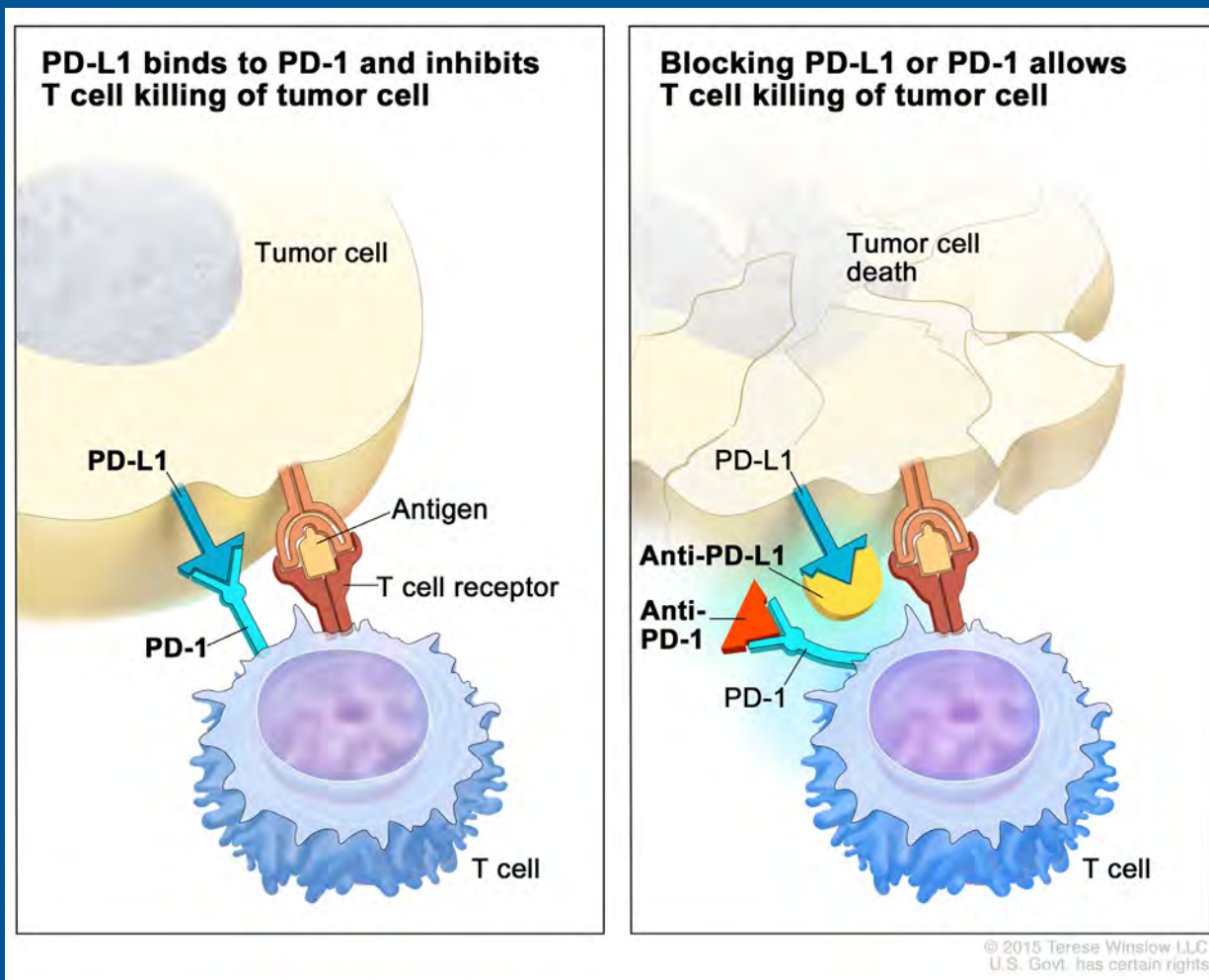
Examples include: Nivolumab (Optivo), Pembrolizumab (Keytruda), Atezolizumab (Tecentriq), Durvalumab (Imfinzi), Avelumab (Bavencio), & Ipilimumab (Yervoy)

Discovered by James Allison, PhD. an Immunologist at the University of Texas MD Anderson Cancer Center. Has since been awarded the **Nobel Prize in Physiology & Medicine**



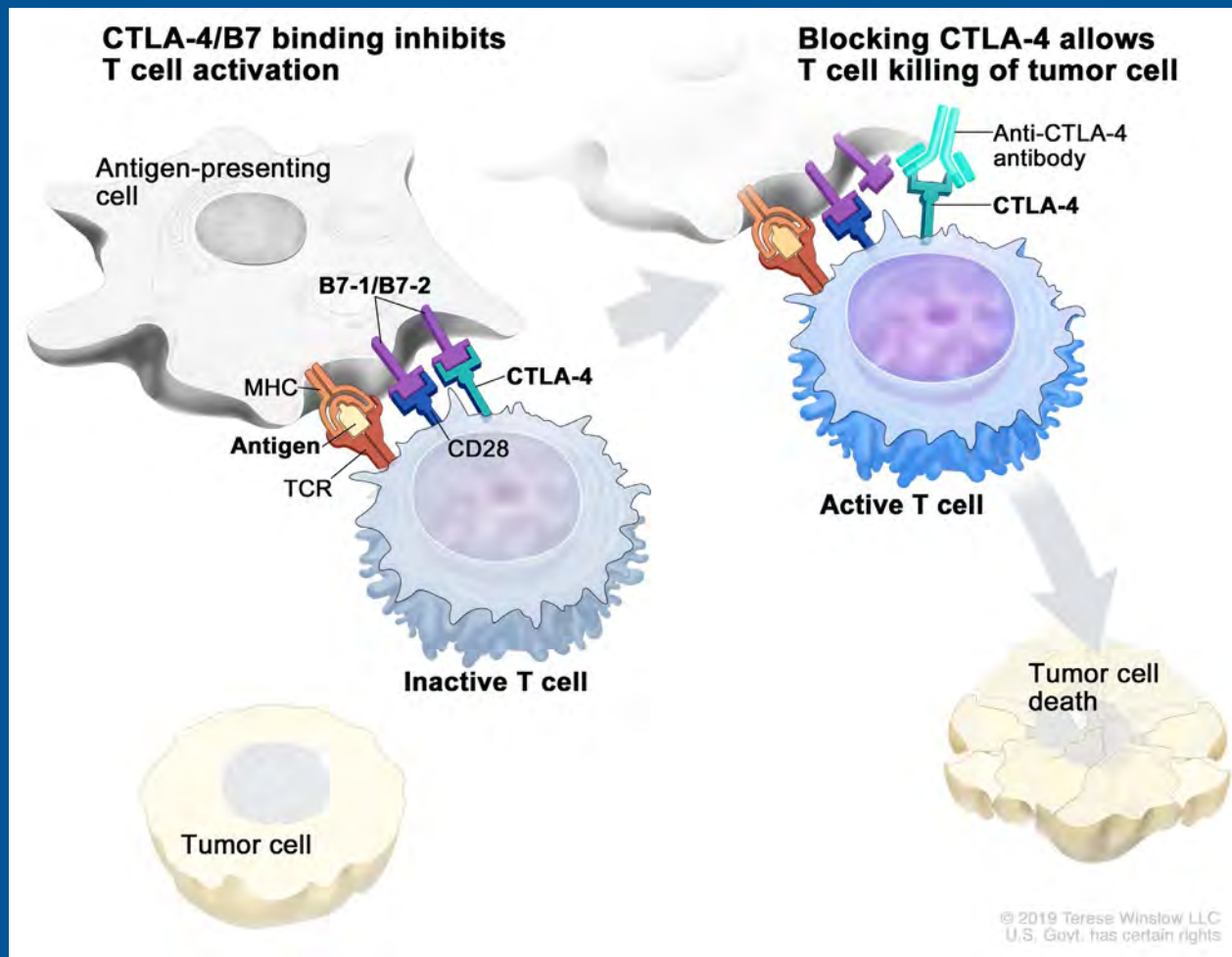
*Source: Google Images for Immunotherapy

Immunotherapy: Checkpoint / PD-1 & PD-L1 Inhibitors



*Source: Google Images for immune & lymphatic system

Immunotherapy: Activated T-Cells (CTLA-4) Inhibitors



*Source: Google Images for immune & lymphatic system

- Many quickly evolving applications of immunotherapies **either alone or in combination with traditional chemotherapy**
- Checkpoint inhibitors in particular have increasingly shown promise and often **significantly favorable survival benefit across multiple solid tumors & blood cancers**
- Examples include:
 - Kidney Cancer
 - Lung Cancer (Non-Small Cell & Small Cell)
 - Skin Cancer (Melanoma)
 - Triple Negative Breast Cancer
 - Liver (Hepatocellular) Cancer
 - Bladder Cancer
 - Hodgkin's Lymphoma
 - Head & Neck Cancers

- In general, **the more genetically unstable the tumor** (rapid turnover, DNA errors, etc.) or **presence of tumor “neo-antigens” generated from tumor-specific mutations** the more likely there will be a stronger response to immunotherapy
- Certain testing may be performed:
 - Microsatellite Instability (MSI) & Mismatch Repair Protein (MMR) Testing
 - Tumor Mutational Burden (TMB)
 - PD-1 / PD-L1 Expression Level

Immunotherapy: Advantages & Disadvantages



- In general, the administration of immunotherapy is easier, shorter, more convenient, less frequent, and overall *less toxic compared to many traditional cytotoxic chemotherapy agents
- Typical side effects are usually very mild (especially with checkpoint inhibitors), and may include fatigue
- Unlike chemotherapy, typically no hair loss or severe nausea or vomiting
- Immunotherapy can affect any organ or system, though some more commonly than others (e.g., thyroid)
- Serious side-effects DO happen and are very important to understand, though overall are rare
- An overactive immune response can lead to autoimmune complications (speak to your oncologist for details)

***NOTE:** Not all immunotherapies are the same, and some are more toxic than others or can cause more serious interactions when used in combination with other systemic cancer therapies or in individuals with pre-existing risk factors (SEE DISCLAIMER).

Immunotherapy (Cont.)

Immunotherapy Video from National Institutes of Health (NIH):

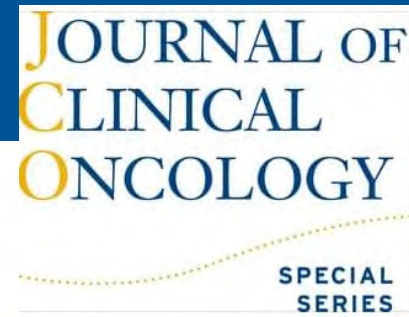
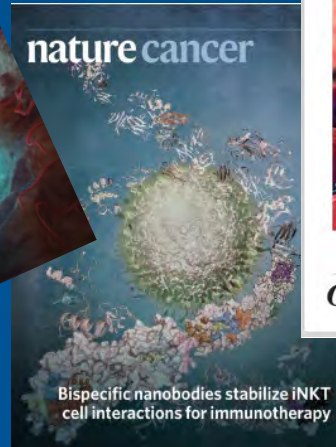
- YouTube: <https://www.youtube.com/watch/jDdL2bMQXfE>



- Testing immunotherapy in earlier stages of cancer (as opposed to Stage IV disease) is actively underway in many clinical trials across many cancer types
- Combining immunotherapy with chemotherapy or with other therapies (e.g., molecular therapy, radiotherapy, etc.) continues to be investigated
- Use of immunotherapy as maintenance to maintain remission or prevent progression is becoming more common
- Immunotherapy often considered as an option for patients who would otherwise not be candidates for aggressive treatment
- New types of immunotherapies and immunotherapy targets are continually being developed everyday
- Cellular therapies (e.g., Adaptive & CAR-T Cell) & Gene Therapy will likely become more widespread as options for difficult to treat cancers in the future
- Concept of “precision medicine” tailored to the patient’s specific tumor and genetics will become more standard



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- Cancer is a significant Global burden, and it is becoming more common
- Cancer is a leading cause of death and disability
- People are living longer and more are surviving cancer
- Importance of screening / early detection cannot be understated
- How we treat cancer continues to evolve, and there are many tools in our toolbox for treating it
- We must appreciate the historical basis for cancer care, and the discoveries that build on the past
- Chemotherapy is still very effective for many cancers, though we are continually trying to find less toxic and effective approaches

- The immune system plays a dynamic role in cancer surveillance, detection, and elimination of cancer. Though cancer often evades the body's defenses
- Immunotherapy harnesses the body's natural immune system to fight cancer and keep it at bay
- Immunotherapy is increasingly used in many types of cancers, and often can be better tolerated than traditional systemic therapies
- The horizon is rich with possibility for exciting new areas of research in immunotherapy such as cellular therapies (e.g., adaptive cell therapy & CAR-T cell therapy), and related gene therapy.
- New areas of scientific research will focus on the tumor microenvironment and tumor genetics to exploit new targets for immunotherapies. It is a rapidly evolving field with a lot of potential!

Learning Objectives Revisited

1. Understand how cancer is changing globally, why it is important to detect cancer early when possible, how cancer care has evolved over time, and key historic breakthroughs in the science of cancer.
2. Develop an appreciation for our body's natural immune system, and its biological role with cancer.
3. Learn what immunotherapy is all about, how it is different than traditional chemotherapy, its advantages for cancer care, and areas for further research.

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Thank You!

