



CLL SOCIETY

Smart Patients Get Smart Care™

UNDERSTANDING IMMUNOLOGY AND CLL

OCTOBER 8, 2026

8:30 AM PT, 9:30 AM MT
10:30 AM CT, 11:30 AM ET

**THIS PROGRAM IS MADE POSSIBLE
THROUGH GENEROUS DONORS AND
GRANT SUPPORT FROM**



SPEAKERS



William Wierda
MD
(SPEAKER)

Clinical Medical Director, Department of Leukemia
Professor, Department of Leukemia
Executive Medical Director, Inpatient Medical Services
The University of Texas MD Anderson Cancer Center



Ed Ratner, MD
(MODERATOR)
CLL Patient Advocate



CLL SOCIETY



CLL SOCIETY

Smart Patients Get Smart Care™

UNDERSTANDING IMMUNOLOGY AND CLL

William G. Wierda, MD, PhD

Professor of Medicine

CLL Section Head

Department of Leukemia

U.T. M.D. Anderson Cancer Center

Houston, TX USA

WHAT IS THE IMMUNE SYSTEM?

The role of the immune system — a collection of structures and processes within the body — is to protect against disease or other potentially damaging foreign bodies.

4 main functions to accomplish this:

Immune Recognition

Immune Effector
Functions

Immune Regulation

Immune Memory



IMMUNOLOGY VOCABULARY

Antibody: (also known as immunoglobulins) Y-shaped proteins that can recognize and bind to antigens, further signaling to others involved in the immune system responses

Antigen: Molecules capable of stimulating an immune response, could be proteins on the surfaces of bacteria, fungi and viruses

Cytokine: Protein involved in cell signaling, especially between immune cells

Cytotoxic: Substance or process that results in cell damage or cell death

Lymphocyte: Type of white blood cell that participates in immunity



TWO MAIN CATEGORIES

Innate Immunity

Specificity

- Non-specific
- No memory

Duration

- Initiates in minutes to hours
- Lasts days to weeks

Components

- The skin & all mucous membranes
- Different defensive white blood cells
- Various substances in blood and body fluids

Adaptive Immunity

Specificity

- Antigen specific
- Has memory

Duration

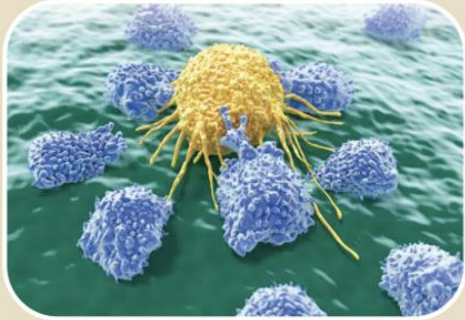
- Initiates in days to weeks
- Lasts months to years

Components

- T and B cells
- Antibodies
- Cytokines

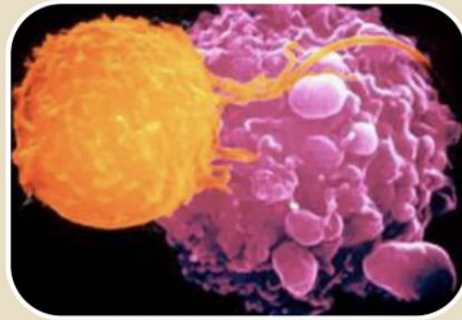


MEET THE PLAYERS



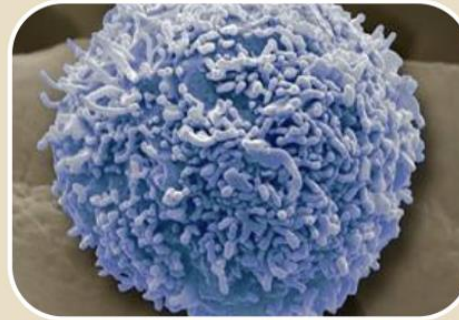
Natural Killer Cells

- **Innate**
- Defend the host from tumors and virally infected cells
- Do not require prior activation
- Release cytotoxic granules that destroy altered cells



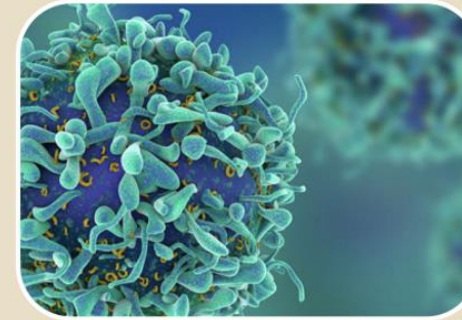
Cytotoxic T-Cells

- **Adaptive**
- Also known as: Killer T-Cells or CD8+
- Produce toxic granules containing enzymes that induce the death of pathogen-infected cells



Helper T-Cells

- **Adaptive**
- Also known as: CD4+
- Produce cytokines to direct an immune response against a pathogen
- Necessary to activate B-cells and Cytotoxic T-Cells

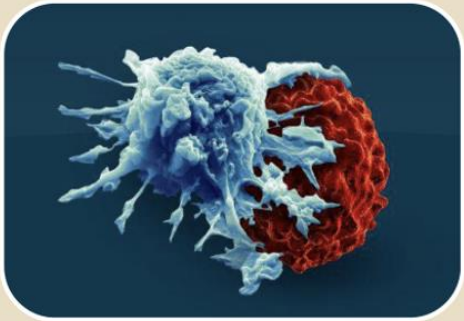


Regulatory T-Cells

- **Adaptive**
- Act to suppress immune response
- Help maintain homeostasis and self-tolerance
- Able to inhibit T-cell proliferation, cytokine production and autoimmunity

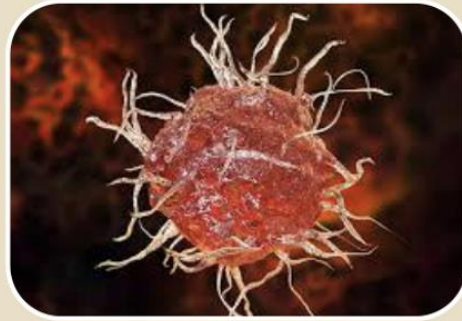


MEET THE PLAYERS



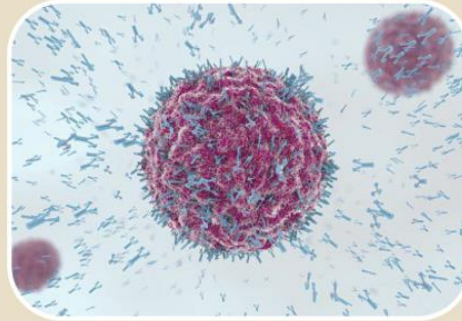
Macrophages

- **Innate**
- Detect, consume by phagocytosis and destroy bacteria and other harmful organisms
- Can present antigens to T-Cells
- Can release cytokines to initiate an inflammation response



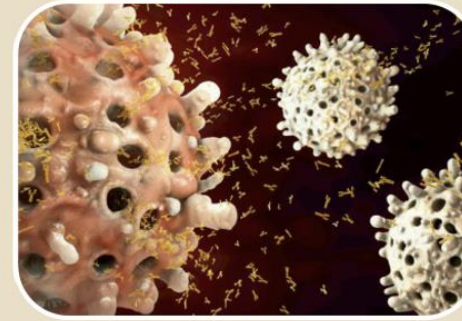
Dendritic Cells

- **Innate**
- Bind and retain antigens to be presented to T-Cells
- Induce the differentiation of germinal B-cells into memory B-cells



Plasma B-Cells

- **Adaptive**
- Activated B-cells that produce antibodies specialized for one pathogen
- Can release several thousands of antibodies in response to an antigen

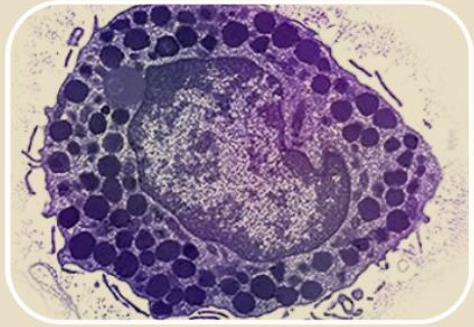


Memory-B Cells

- **Adaptive**
- Important for maintaining immunity
- Makes any secondary exposures to an antigen quicker (and possibly stronger), sometimes before you even feel sick again

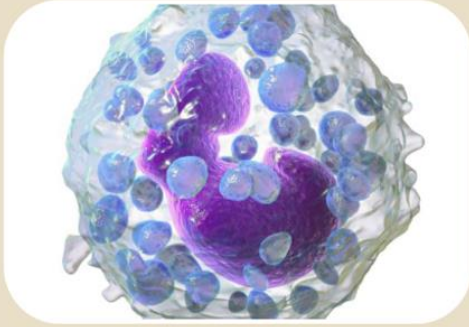


MEET THE PLAYERS



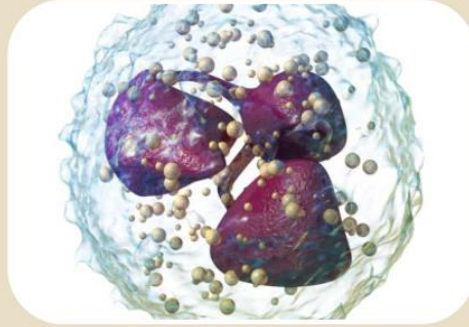
Mast Cells

- **Innate**
- Carry granules containing histamine and heparin
- Play a role in the inflammatory process



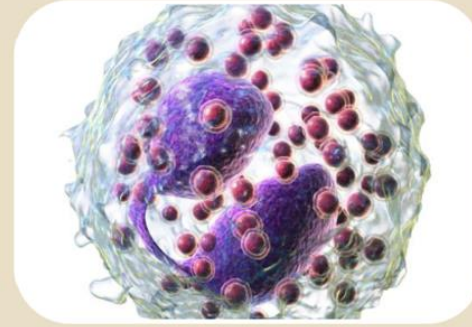
Basophils

- **Innate**
- Important for allergic and antigen response
- Excrete histamine and heparin
- Can also release chemical signals to attract eosinophils and neutrophils to an infection site
- *Lifetime* : Hours to days



Neutrophils

- **Innate**
- Usually first responder to a microbial infection
- Active in the phagocytosis of bacteria and can be found in pus
- Effective against bacterial or fungal infections
- *Lifetime* : Hours to days



Eosinophils

- **Innate**
- Responds to allergies, parasitic infections, collagen diseases, and diseases of the spleen and central nervous system.
- Secretes chemicals to destroy large parasites
- *Lifetime* : 8-12 days



MANIFESTATIONS OF IMMUNE DYSFUNCTION IN CLL

Vaccinations

- **Infection risk**
 - Increased risk for infection – bacterial, viral, less fungal
 - Low antibody levels (IgG)
 - Poor response to vaccination

Cancer Screening

- **Risk of other cancers**
 - Skin, breast, prostate, colon
- **Autoimmunity (AIHA, PRCA, and ITP)**
- **Reduced effectiveness of immune-based treatments**



VACCINATIONS – MYTH VS. FACT

MYTH!

- People with CLL should not receive any vaccinations, ever.
- People with CLL don't respond as well to vaccinations. **FACT!**
- People with CLL shouldn't receive vaccinations while in the middle of chemo/immunotherapy. **FACT!**
- Vaccines can give you the infection you're trying to prevent (Flu / COVID19). **MYTH!**

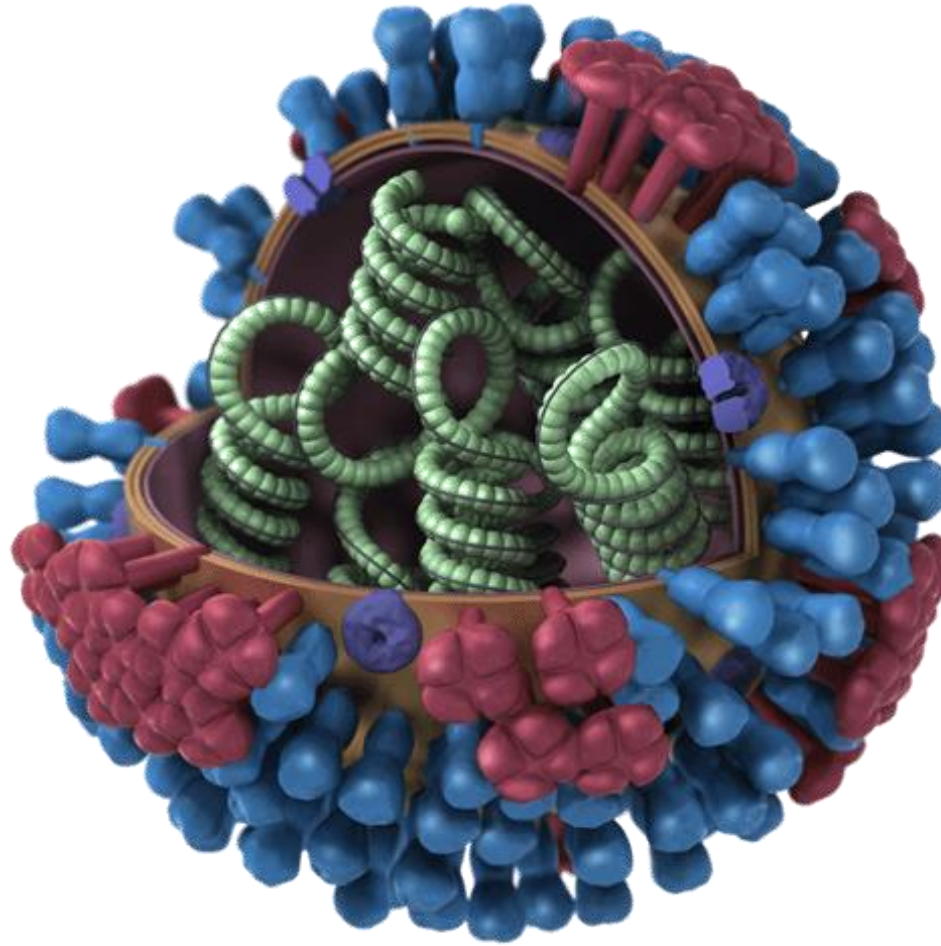


VACCINES CLL PATIENTS SHOULD NOT RECEIVE

These include:

- MMR +/- varicella
- Rotavirus
- Smallpox
- Varicella (Varivax)
- Yellow fever
- Zostavax (Zoster)
- FluMist (nasal flu vaccine)
- Live oral typhoid
- BCG
- Oral polio
- Rotavirus
- Replicating smallpox vaccine

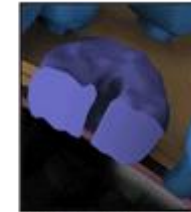
VACCINATIONS: INFLUENZA



Hemagglutinin



Neuraminidase



M2 Ion Channel



RNP



VACCINATIONS: INFLUENZA

- Vaccinate by end of October each year
- Don't vaccinate during an acute infection
- Don't vaccinate in the middle of CD20 mAb or chemotherapy
- It takes 2 weeks for antibodies to develop
- No proven benefit to getting a “booster” mid-season
- CDC has no official recommendation of one vaccine over another
 - Age ≥ 65 yrs – Fluzone High-Dose Trivalent; Flublok Trivalent, Fluad Trivalent
 - Age < 65 yrs – inactivated IIV3 or recombinant RIV3

VACCINATIONS: INFLUENZA

Types of Flu Vaccines

- Inactivated or recombinant are safe and effective
 - Flublok Quadrivalent (recombinant): only egg-free vaccine
 - Fluzone Quadrivalent: inactivated, protects against 2 Flu A and 2 Flu B viruses
 - Fluad Quadrivalent: inactivated with an adjuvant (MF59) to enhance immune response; approved for >65
- Live attenuated (or weakened; aka nasal spray/FluMist) is **NOT** safe for CLL patients.

Regular v. High Dose

- Fluzone High Dose Quadrivalent (inactivated); contains 4x the antigen of standard-dose; approved for ≥65



VACCINATIONS: HERPES ZOSTER/SHINGLES

- Painful, blistering rash; occurs unilaterally, following “dermatomal” (underlying nerve) distribution pattern
- Results from reactivation of varicella-zoster virus from deep nerve roots
- 10-13% of those who develop shingles will get post-herpetic neuralgia (PNH), lasting weeks to years following infection



VACCINATIONS: HERPES ZOSTER/SHINGLES

- Nearly 1/3 of Americans will develop shingles in their lifetime
- Any type of cancer is associated with a 40% increased risk of developing shingles
- Blood cancers had the highest risk: **>3 times that of those without cancer**
- Shingles infection can be seen as a marker of underlying malignancy



VACCINATIONS: HERPES ZOSTER



VACCINATIONS: HERPES ZOSTER



VACCINATIONS: HERPES ZOSTER

Shingrix (Recombinant Zoster Vaccine; RZV)

- Approved in 2017; recommended for immunocompetent adults 50 and older
- Safer and more effective than Zostavax (ZVL); recommended regardless of prior Zostavax vaccination
- Pooled efficacy of 2 large trials: 92% effective in preventing shingles
- Antibody response in CLL patients may be slightly less for both treatment naïve and those on BTKi

Administration

- Requires 2 doses, 2-6 months apart
- Can receive at same time as flu or pneumococcal vaccinations
- Should not be given during acute shingles infection
- No need to screen for prior varicella exposure
- Should be given even for those who received chicken pox vaccination



VACCINATIONS: PNEUMOCOCCUS



VACCINATIONS: PNEUMOCOCCUS

Protects against infection with ***Streptococcus pneumoniae***, a significant human pathogenic bacteria.

- Pneumococcal polysaccharide (PPSV23; Pneumovax 23); since 1983 – protection wanes over 5-6 years (induces immune response via release of immunoglobulins from B cells)
- Pneumococcal conjugate vaccine (PCV13; Prevnar 13); since 2010 (T cell-dependent mechanism, resulting in durable memory B cell formation)
- Pneumococcal conjugate vaccine 15 (PCV15; Vaxneuvance); approved 2021; effective against same 13 serotypes as PCV13.
- Pneumococcal conjugate vaccine 20 (PCV20; Prevnar 20); approved 2021; effective against all serotypes of PCV13 and 6 of 7 serotypes in PPSV23.



PNEUMOCOCCAL PNEUMONIA VACCINATION - NAIVE

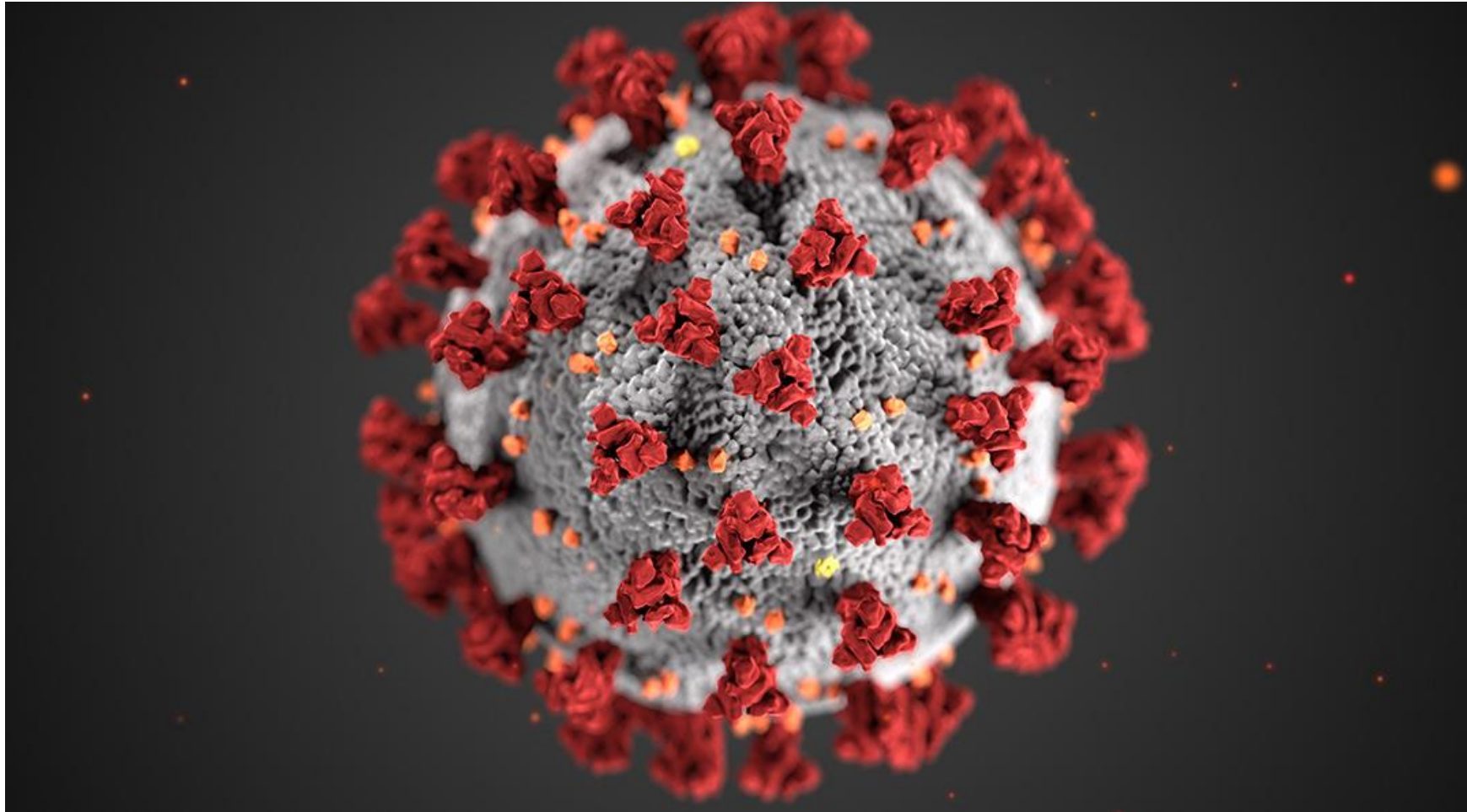
Vaccine	Schedule	Further pneumococcal vaccine?
PCV20	1 dose	No
PCV21	1 dose	No
PCV15 → PPSV23	PCV15, then PPSV23 normally ≥ 1 year later; minimum 8 weeks for immunocompromised patients	Series then complete

PNEUMOCOCCAL PNEUMONIA VACCINATION - PRIOR

This is increasingly relevant for CLL patients vaccinated under the older PCV13/PPSV23 schedules (from CDC):

- PPSV23 only: give PCV20, PCV21, or PCV15 ≥ 1 year later. If PCV15 is used after prior PPSV23, another PPSV23 is not required.
- PCV13 only: give PCV20 or PCV21 ≥ 1 year later. The series is then complete.
- PCV13 + one PPSV23 in an immunocompromised adult: give PCV20 or PCV21 ≥ 5 years after the most recent pneumococcal vaccine. The series is then complete.
- For adults ≥ 65 who previously completed PCV13 + PPSV23 with PPSV23 given at ≥ 65 , an additional PCV20 or PCV21 ≥ 5 years later is based on shared clinical decision-making.

VACCINATIONS: COVID-19



COVID-19 VACCINATION – YES, WE ARE STILL RECOMMENDING IT FOR OUR PATIENTS!

Protective response rate may be lower in CLL, regardless of treatment status, but especially those receiving CD20 antibody or on B-cell pathway inhibitors. Vaccine response rates improve with boosting. T cell activation by vaccination enhances viral clearance and minimizes severity of symptoms.

- **Moderna or Pfizer (mRNA):** 3 primary doses (3-4 weeks apart), followed by bivalent booster dose at least 8 weeks following primary series.
- **Janssen:** if received J&J vaccine initially, should receive a second dose with monovalent mRNA vaccine (at least 4 weeks later), then bivalent booster at least 8 weeks later.
- **Nuvaxovid (protein):** 2 primary doses (3 weeks apart), followed by bivalent booster at least 8 weeks later.

What about Evusheld??

As of Jan 26, 2023, Evusheld is no longer authorized for use in US as current SARS-CoV-2 variants are resistant.

VACCINATIONS FOR PATIENTS WITH CLL

Vaccine	Recommendation in CLL	Practical comments
Influenza	Every year	Use inactivated or recombinant vaccine, not intranasal live vaccine. Patients ≥65, high-dose/adjuvanted/recombinant vaccine is generally preferred.
Recombinant zoster (Shingrix/RZV)	Yes—2 doses	Recommended for immunocompromised adults ≥19 years, regardless of previous shingles or chicken pox vaccine. This is a non-live vaccine.
Pneumococcal	Strongly recommended	Current conjugate vaccines preferred. For a vaccine-naïve CLL patient, a single PCV20 or PCV21 is generally the simplest contemporary strategy; PCV15 followed by PPSV23 is another option. Prior PCV13/PPSV23 vaccination requires individualized catch-up.
RSV	Yes when age/risk eligible	Particularly relevant in CLL because of respiratory infection risk. Current CDC recommendations include adults ≥75, and adults 50–74 at increased risk; immunocompromise is an important risk factor.
COVID-19	Yes	Follow the current CDC schedule for moderately/severely immunocompromised persons, rather than the routine immunocompetent schedule. Nuvaxovid
Tdap/Td	Routine	Tdap once if not previously received, then Td or Tdap every 10 years, plus wound indications.
Hepatitis B	Risk/age based	Particularly relevant before immunosuppressive therapy because of HBV reactivation considerations.
Hepatitis A	If otherwise indicated	Travel, chronic liver disease, exposure risk, etc.



IMMUNOGLOBULIN REPLACEMENT

- Hypogammaglobulinemia (HGG) occurs in 85% of all CLL patients, leading increased risk of infection – respiratory tract, skin, urinary
- Risk of infection increases when IgG level falls <500 gm/dL
- Treatment of CLL generally does not correct HGG
- Treatment with Ig replacement (IVIG or subQ injections) shown to reduce risk of recurrent severe bacterial infections in CLL
- Does not replace IgA or IgM
- Who should get it ?
- Recurrent infection AND IgG <500 gm/dL
- Maintain IgG >500 gm/dL at nadir
- Winter months



IMMUNE SYSTEM FAILURES – CANCER

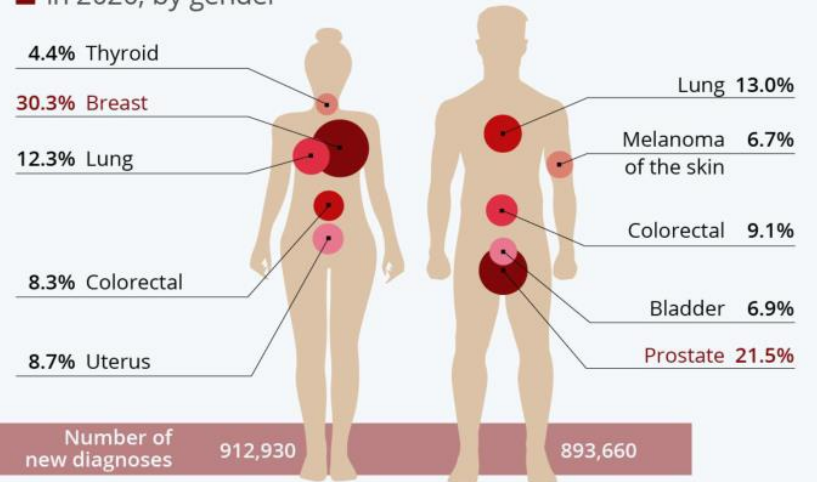
Cancer is a very large and broad term that can be summed up as a disease where the *“body’s cells begin to divide without stopping and spread into surrounding tissues.”*

Usually, the immune system can regulate cell survival and production. However, cancer sees old or damaged cells surviving, and new cells forming when they are not needed.

The greatest challenge with cancer is the immune systems inability to recognize cancer, as the cancerous cells “hide”.

The Most Common Types of Cancer in the U.S.

Projected share of new cancer diagnoses in the U.S. in 2020, by gender



Source: American Cancer Society



statista



CLL SOCIETY

SCREENING FOR OTHER CANCERS

- Second malignancy screening: Patients with CLL have an increased risk of other primary malignancies, particularly skin cancers.
- Perform or refer for a full-body skin examination at diagnosis and at least annually thereafter, with counseling regarding sun protection and skin self-examination.
- Ensure adherence to age-, sex-, exposure-, family-history-, and risk-appropriate screening for colorectal, breast, cervical, prostate and lung cancers according to current population guidelines.
- Additional imaging or laboratory screening for second malignancies is not routinely recommended in asymptomatic patients.
- Multi-cancer early detection testing - no recommendation....yet (Galleri, Cancerguard, Caris Detect)

CANCER SCREENING

According to ACS, patients with CLL are at higher risk of skin cancer (all types), as well as cancers of larynx, lung, colon and soft tissue sarcoma. Following treatment with chemoimmunotherapy, risk of secondary MDS/AML is 5-6%.

- Skin cancer
Annual skin exams with a dermatologist
- Breast cancer
Annual MMGs for women 45-54; every 2 years 55 and older
- Colorectal cancer
Colonoscopy every 5-10 years (depending on risk and history)
- Prostate cancer
PSA and physical exam
- Lung cancer
Low-dose CT scan recommended age 55-74 with 30-pk-yr history of smoking.



BREAST CANCER SCREENING – AVERAGE RISK

Age	USPSTF	American Cancer Society (ACS)	ACR/SBI
<40	No routine mammography	No routine mammography	No routine mammography for average risk
40–44	Every 2 years	Option for annual mammography	Annual mammography
45–54	Every 2 years	Annual mammography	Annual mammography
55–74	Every 2 years	Every 2 years or annually	Annual mammography
≥75	Evidence insufficient	Continue if in good health and life expectancy ≥10 years	Continue unless severe comorbidity limits life expectancy



IMMUNOENGINEERING APPLICATIONS – CANCER THERAPY

There are numerous cancer therapies out, or in-the-making.

The newer approaches commonly used are the following:

1. Adoptive Cell Therapy:

- *Expanding immune cell numbers or genetically modifying*

2. Cancer Vaccines :

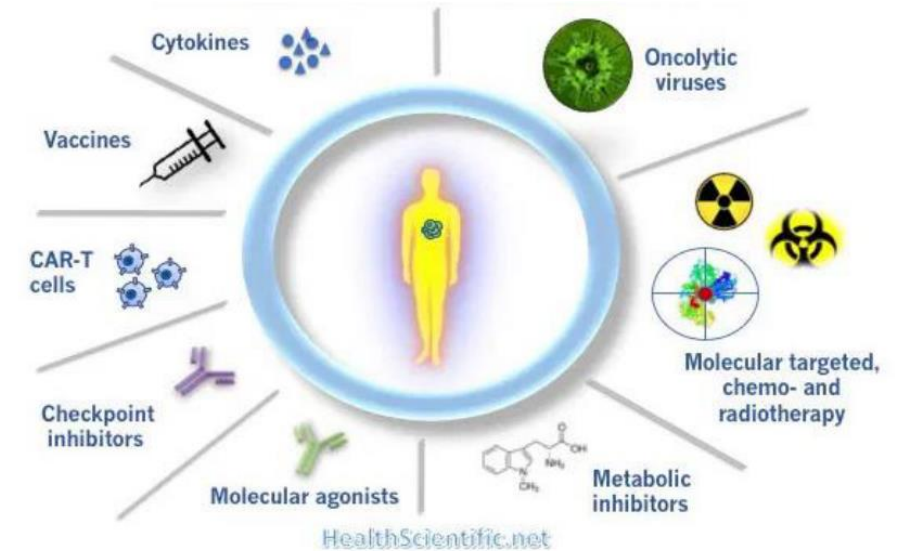
- *Educate the immune system about what cancer cells “look like”*
- *Mainly for prevention*

3. Immunomodulators :

- *Modulates “brakes and gas pedals” of the immune system*

4. Targeted Antibodies:

- *Creating and customizing antibodies against specific cancer targets*



**Carnegie
Mellon
University**

IMMUNE-BASED CANCER THERAPIES

- **Immune checkpoint inhibitors**
 - PD-1, PD-L1, CTLA-4, LAG-3
- **Tumor-targeting mAbs**
 - CD20, CD38, HER2, EGFR
- **Bi- multi-specific immune-cell engagers**
 - CD19xCD3, CD20xCD3
- **CAR-T cell therapy**
 - CD19, BCMA
- **Engineered T-cell therapy**
 - TCR-engineered
- **Tumor-infiltrating lymphocytes**
- **NK-cell-based therapy**
 - CAR-NK, NK engagers
- **Cancer vaccines**
 - Dendritic-cell, peptide, mRNA
- **Oncolytic virus**
- **Cytokine-based**
- **Innate immune agonists**
- **Immunomodulating drugs**
 - Lenalidomide, pomalidomide



WHAT ARE WE WORKING ON AT MDACC?

Harrison Project – Cure CLL – Immune-restoration and vaccination

- Understanding immune restoration in patients in remission (uMRD)
- Timing of immune restoration with current targeted treatments
- Identifying drugs / agents that actively restore immune function
- Developing CLL vaccines to train immune system to prevent return of CLL
- Curative strategy: targeted therapy → immune-effector (residual disease) → CLL vaccine
- Reducing infection risk and risk of other cancers

THANK YOU!

wwierda@mdanderson.org



CLL SOCIETY

**THIS PROGRAM IS MADE POSSIBLE
THROUGH GENEROUS DONORS AND
GRANT SUPPORT FROM**



THANK YOU FOR ATTENDING!

Please take a moment to complete our post-event survey,
your feedback is important to us

If your question was not answered,
please feel free to email: trustedcare@cllsociety.org

Join us for our next virtual event,
**ASK ME ANYTHING FEATURING DR. DANIEL ERMANN AND DOREEN
ZETTERLUND**
NOVEMBER 16

CLL SOCIETY is invested in your long life. Please invest in
the long life of the CLL SOCIETY by supporting our work:
cllsociety.org/donate-to-cll-society/



CLL SOCIETY