Biologics for the Treatment of Immune Mediated Inflammatory Disease (Autoimmune Disease)

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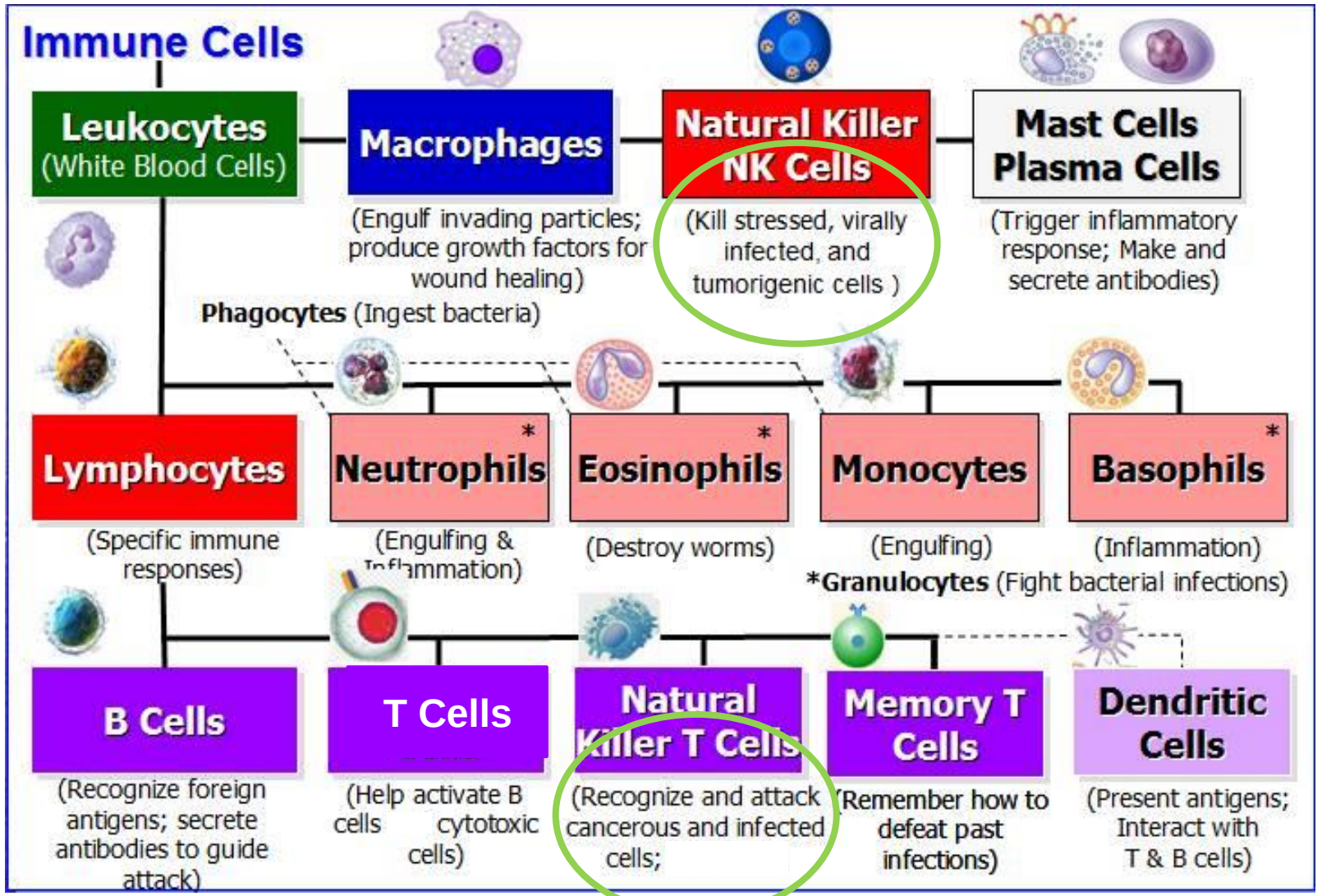
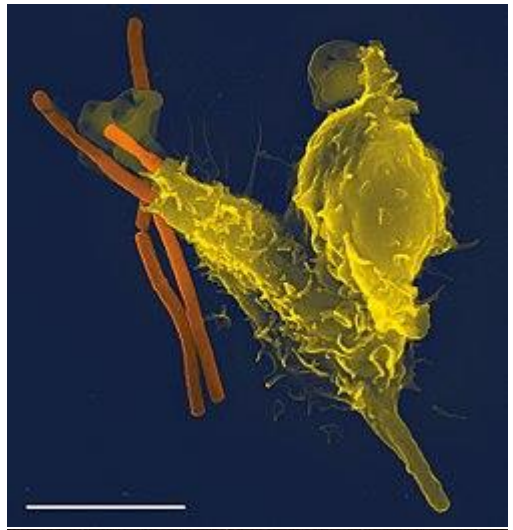
Overview of the Immune System

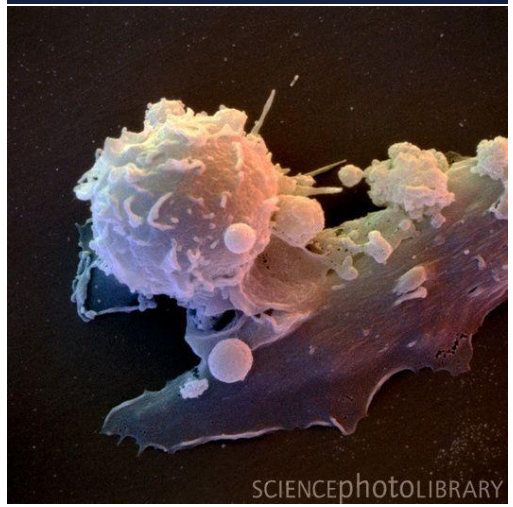
- The immune system is our body's defense
  - It eliminates potentially harmful foreign molecules, cells, and organisms from the body.
  - The immune system also has the capacity to recognize and destroy abnormal cells that derive from host tissues i.e. tumor cells
  - The immune system can distinguish self antigens from foreign ones
- Successful immune defense requires activation, regulation, and resolution of the immune response
  - The immune system is activated when the foreign antigen is recognized by circulating antibodies or cell surface receptors and/or when damaged, injured or stressed cells send out alarm signals in the form of cytokines and/or eicosanoids
  - The immune response must be regulated to prevent overwhelming damage to the host
  - The immune response resolves when foreign antigen is sequestered or eliminated from the body. There is no immune response without antigen stimulation

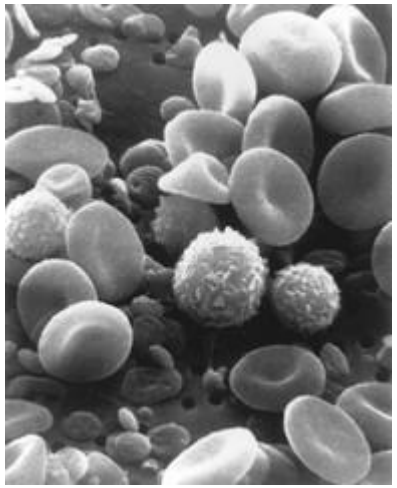
https://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/overview-of-the-immune-system

Cells of the Immune System and How They Work









http://deathtodiabetes.blogspot.com/2015/08/immune-system.html?_sm_au_=iVVZPQqN71232b5J#.XBGIqXRKg2w

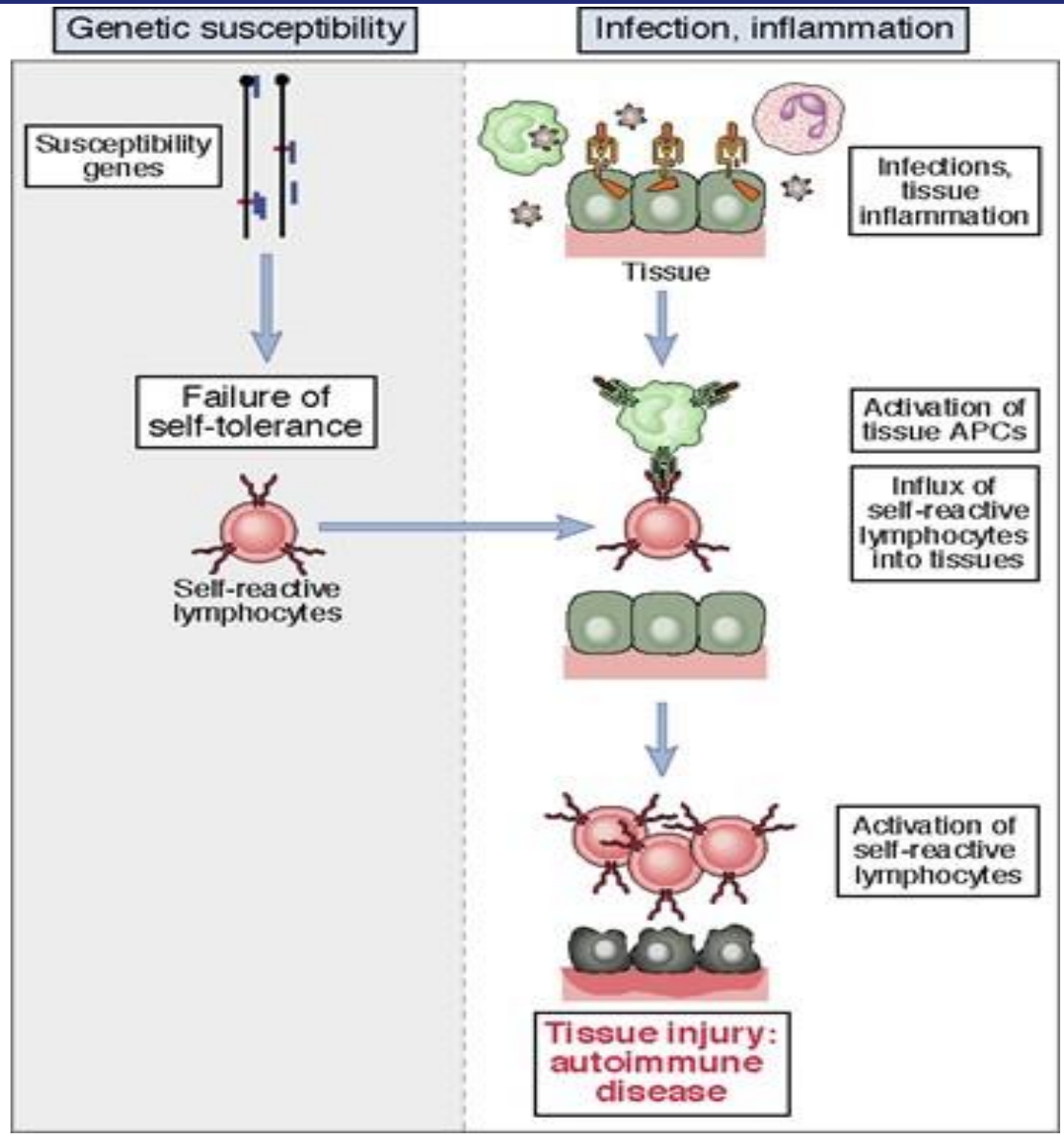
https://en.wikipedia.org/wiki/Immune_systeme

Acute vs Chronic Inflammation

	acute	chronic
Initiators	Microbial surfaces & fragments Injured tissue & tissue fragments	Non-digestible organisms Non-degradable foreign matter Auto-immune reactions
Mediators	Mast cell products (histamine) Bradykinin Lysosomal components Lipid mediators	T-lymphocyte & macrophage products: cytokines & GF Proteases and reactive oxygen Complement, Lipid mediators
Cell Populations	Neutrophils Macrophages	T-lymphocytes, plasma cells Macrophages Fibroblasts
Time Course	Acute onset, days	Insidious onset: weeks-years
Outcome	Resolution, Abscess formation Chronic inflammation	Tissue destruction; fibrosis

Pathogenesis of Autoimmune Disease

- Autoimmune diseases are a broad category of related diseases in which the person's immune system attacks his or her own tissue
- Failure of mechanisms to control reactions against self antigens is the underlying cause for autoimmune disease
- Autoimmune disease is self-perpetuating due to persistence of self-antigens and redundancy in inflammatory pathways
- Autoimmune inflammatory response is amplified by cytokines



https://www.google.com/search?q=pathogenesis+of+autoimmunity+image&tbm=isch&tbs=rimg:CT7R7d7bnCGpIjgTaXtYnkVMTtL-S9pqK-4uzQHJGO4JD-mo2cCWin0Nlnn9SMn2QZlsVFsv23W5B98FXIOs7iTVq9VCoSCRNpe1ieRUxOEUpZGJRf9cUpKhIJ0v5L2mor7i4RLz2jsDX50eoqEgnNAckY7gkP6REkKCmRqSEMAioSCajZwJbQ2WefERkOztYeT_18WKhIJ1IyfZBmWxUURvDyUTu1R4NQqEgmy_1bdbkH3wVRF0cktlkeCa6ioSCcg6zuJNWr1UEWeejL1Dj6W3&tbo=u&sa=X&ved=2ahUKEwiZ3qfsibbeAhVqTd8KHa0mALYQ9C96BAgBEBg&biw=1680&bih=908&dpr=1#imgrc=iZVvj9GTxUDzyM:

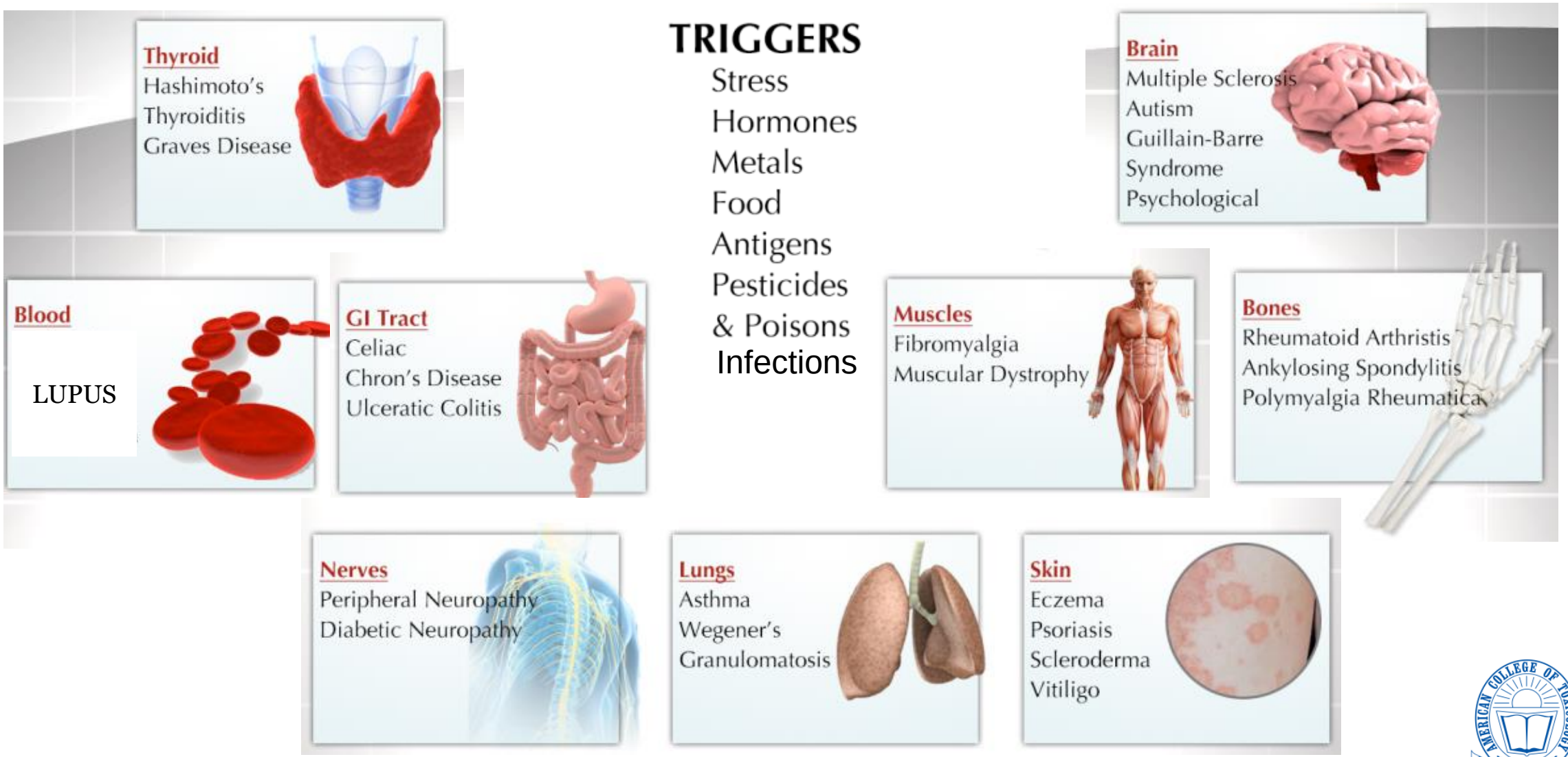
American College of Toxicology Signature Webinar

What a Patient with Autoimmune Disease Experiences…

- Chronic, progressive disease with symptoms that come and go in the form of flares
  - Inflammation, pain, muscle aches, fatigue, rash, and a low-grade fever
  - Severity of the flare varies and may worsen with time
  - Symptoms depend on which part of the body is affected which can vary even within a disease.
- There are at least 50 million Americans living with an autoimmune disease, of whom 75% are women
- Autoimmune disorders can target specific types of tissue or particular organs
  - e.g. blood vessels, skin, or cartilage

https://www.verywellhealth.com/what-is-an-autoimmune-disease-189661

Organ Specific Autoimmune Disorders



Presentation Outline

- What is the Standard of Care for treatment of Autoimmune Disease?
- Biologics for the treatment of autoimmune disease
- The process for developing a novel biologic
- What about combinations?
- What can go wrong with chronic administration?

Current Sequence of Therapy for Autoimmune Disease (1)

- First-Line: Disease-modifying antirheumatic drugs (DMARDs)
- Immunosuppressive drugs other than glucocorticoids used in the treatment of various rheumatologic conditions to achieve one or more of the following goals:
  - To induce or maintain a remission
  - To reduce the frequency of flare or relapse
  - To allow tapering of glucocorticoids while maintaining disease control
- Most DMARDs are generic small molecule-based agents
  - Common DMARDs: methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide
  - Initially may be used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids which provide faster relief from ongoing symptoms
  - Usually effective for many years in the general autoimmune population but often fail to elicit an adequate long-term response
  - DMARDs can stop working for unknown reasons
    - Possibilities include increased disease activity and recognition of DMARD as a foreign substance and subsequent clearance from the circulation

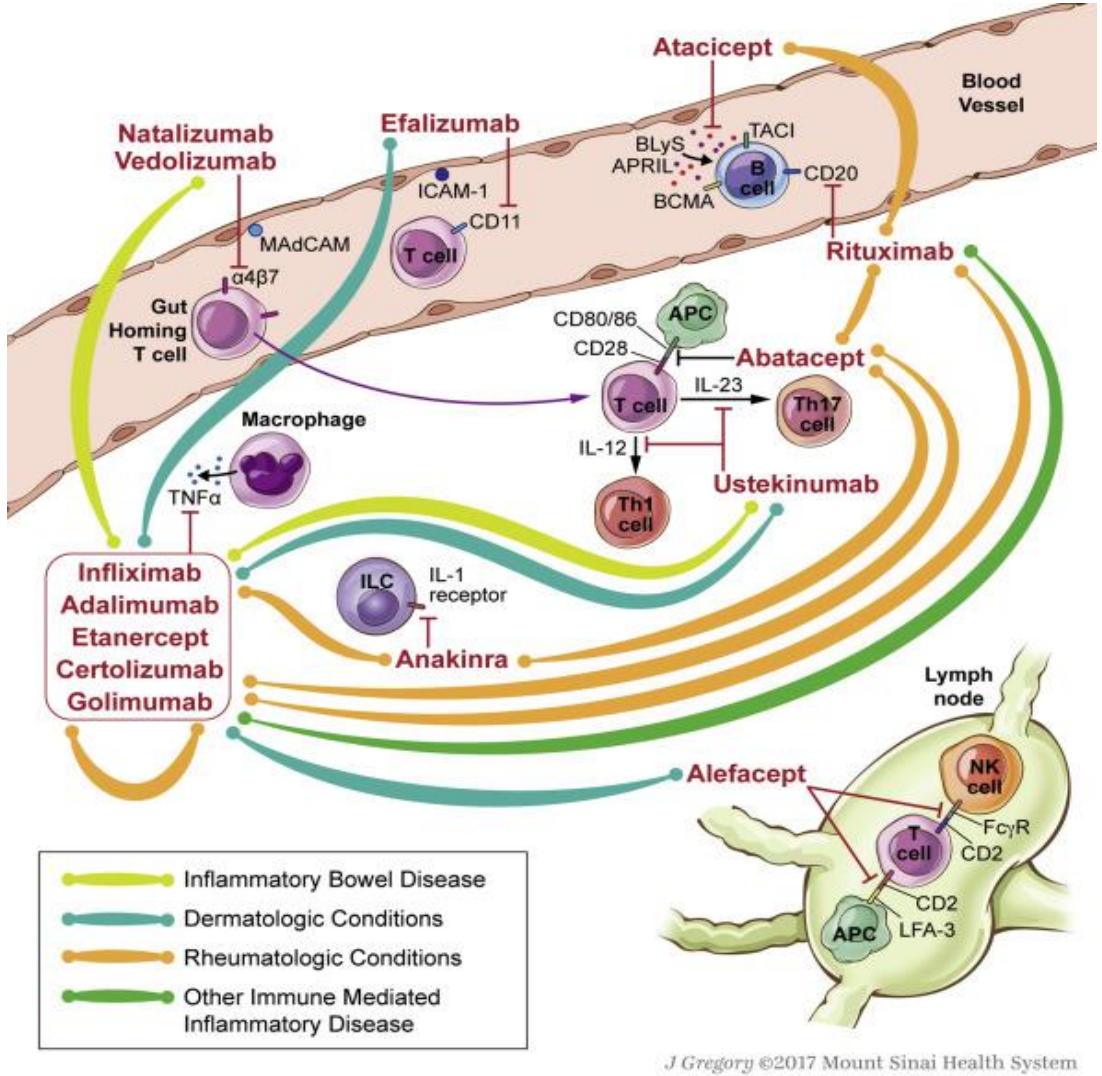
Current Sequence of Therapy for Autoimmune Disease (2)

- Second-Line: Biologics
- Most biologics are very large, complex molecules (eg. proteins, monoclonal antibodies) or cocktails of molecules
  - Examples of approved monoclonal antibodies for IMIDs include:
    - TNFα inhibitors (etanercept/Enbrel, adalimumab/Humira, infliximab/Remicade, certolizumab pegol/Cimzia, golimumab/Simponi)
    - Other approved biologics with different targets (anakinra/Kineret, abatacept/Orencia, rituximab/Rituxan, and tocilizumab/Actemra)
  - Biologics may be used in combination with each other or in combination with DMARDs

https://www.uptodate.com/contents/disease-modifying-antirheumatic-drugs-dmards-beyond-the-basics

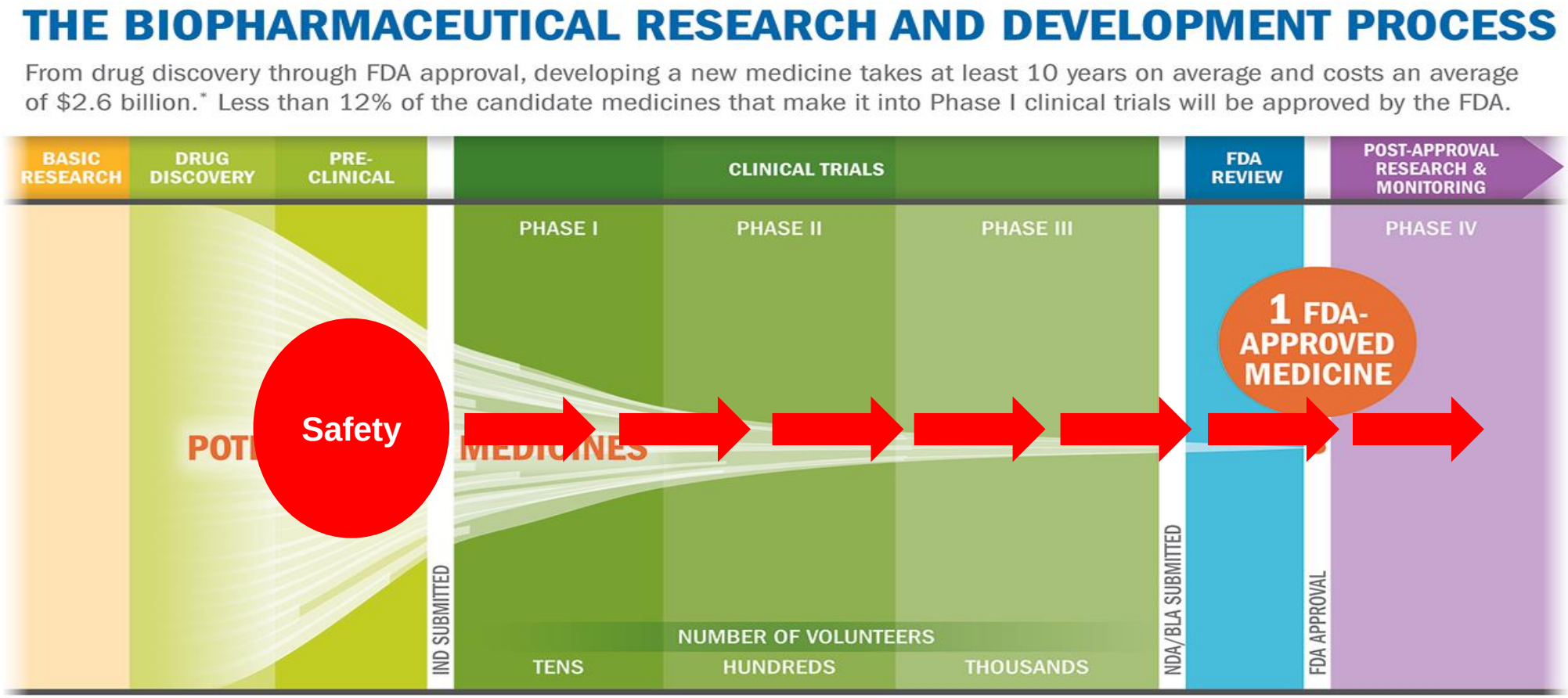
Biologics Used to Combat Autoimmune Pathogenesis

- Biologics target specific components of both the anti-self immune response and the inflammatory cascade
- Over the years, the therapeutic goal in IMID has shifted during recent years from control of symptoms toward achieving clinical remission and tissue healing to prevent disease progression



PMID: 29481970

How Is a Novel Biologic Developed?



https://www.phrma.org/graphic/the-biopharmaceutical-research-and-development-process

Nonclinical Safety Assessment Program for Novel Biologics Includes…

ICH S6

- Nonclinical safety assessments conducted in the “relevant species”
  - The test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)
- The product should be comparable to that proposed for the initial clinical studies
  - Process to remove host cell proteins and other contaminants
  - Immunological properties of the antibody should be described in detail, including its antigenic specificity, complement binding
  - Tissue Cross Reactivity to define any unintentional reactivity and/or cytotoxicity towards human tissues distinct from the intended target.
- Data package may include (but is not limited to):
  - Evaluation of exposure and PK
  - Single dose tox studies
  - Repeat dose tox studies with recovery
    - To establish the NOAEL and safety margin
  - Immunotoxicity Assessments
    - For biologics that modulate/inhibit the immune system
  - Safety Pharmacology

What about Safety Assessment of Combinations of Biologics?

FDA Guidance, "Nonclinical Safety Evaluation of Drug or Biologic Combinations"

- Combination of two or more previously marketed biologics
  - Generally, sufficient clinical and nonclinical data will exist for each drug product separately
  - The indications for which each drug is marketed should be compared to those for which the combination is being proposed
    - For example, drug products marketed for acute use may not have nonclinical data to support chronic use
  - To the extent that there are gaps in the data, the FDA may recommend that additional nonclinical studies be conducted
- Combination of previously marked biologic(s) with a novel biologic
  - Nonclinical studies should be conducted on the new biologic(s) for a product
  - The standard battery of nonclinical studies as described in ICH S6 generally will be appropriate
  - Depending on the duration of the proposed therapy, the FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination in the most appropriate species
  - Exposure to the drugs/biologics be at ratios that are relevant to the intended clinical use
- Combination of novel biologics
  - The standard battery of nonclinical studies in the relevant species as described in ICH S6 should be conducted for each novel biologic
  - Additional data may be obtained from studying the combination in appropriate animal models of efficacy, if considered relevant
    - For example, one drug has been shown to alter the efficacy of the second drug
  - Combination PK, combination safety pharmacology studies, combination local tolerance studies may be necessary

What Happens with Chronic Administration of Immune Suppressive and/or Anti-Inflammatory Biologics?

- Immunotoxicity
- Increased Risk of Infection
  - Monitor in the clinic
- Immunogenicity
  - Host develops ADA to the biologic
- Carcinogenicity / Malignancy Risk
  - Immune system plays a significant role in elimination of tumor cells
- How are adverse findings managed by Regulators?

Examples of Labels for Biologics Approved to Treat Autoimmune Disease

Rituxan (rituximab)
Injection for Intravenous Use
Initial U.S. Approval: 1997

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.

- **Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).**

HUMIRA® (adalimumab) injection, for subcutaneous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):
- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

ENBREL® (etanercept) injection, for subcutaneous use
ENBREL® (etanercept) for injection, for subcutan
Initial U.S. Approval: 1998

WARNING: SERIOUS INFECTIONS and M
See full prescribing information for complete

SERIOUS INFECTIONS
- **Increased risk of serious infections leading to h death, including tuberculosis (TB), bacterial se infections (such as histoplasmosis), and infectic opportunistic pathogens. (5.1)**
- **Enbrel should be discontinued if a patient deve**

CIMZIA (certolizumab pegol) for injection, for subcutaneous use
CIMZIA (certolizumab pegol) injection, for subcutaneous use
Initial U.S. Approval: 2008

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.
- **Increased risk of serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens (5.1).**
- **CIMZIA should be discontinued if a patient develops a serious infection or sepsis (5.1).**

t treatment for TB
treatment, even if
fatal, have been
ts treated with TNF
5.2). CIMZIA is not
)

TYSABRI (natalizumab) injection, for intravenous use
Initial U.S. Approval: 2004

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)**
- **Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI (5.1)**
- **Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)**
- **Because of the risk of PML, TYSABRI is available only through a restricted distribution program called the TOUCH® Prescribing Program (5.1, 5.2)**

AMERICAN COLLEGE OF TOXICOLOGY
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What's Been Covered…

- Immune System and its role in the Autoimmune Disease process
- Current therapies for Autoimmune Disease
- Nonclinical Safety Program
- Safety evaluation when combining therapeutics
- What the labels show

The talks that follow will explore:

- The potential adverse effects of these immune suppressive / anti-inflammatory biologics on the Immune System
- The risks for Carcinogenicity
- How Regulators address adverse findings

Acknowledgments

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