

# INFLAMMATION

## A Primer

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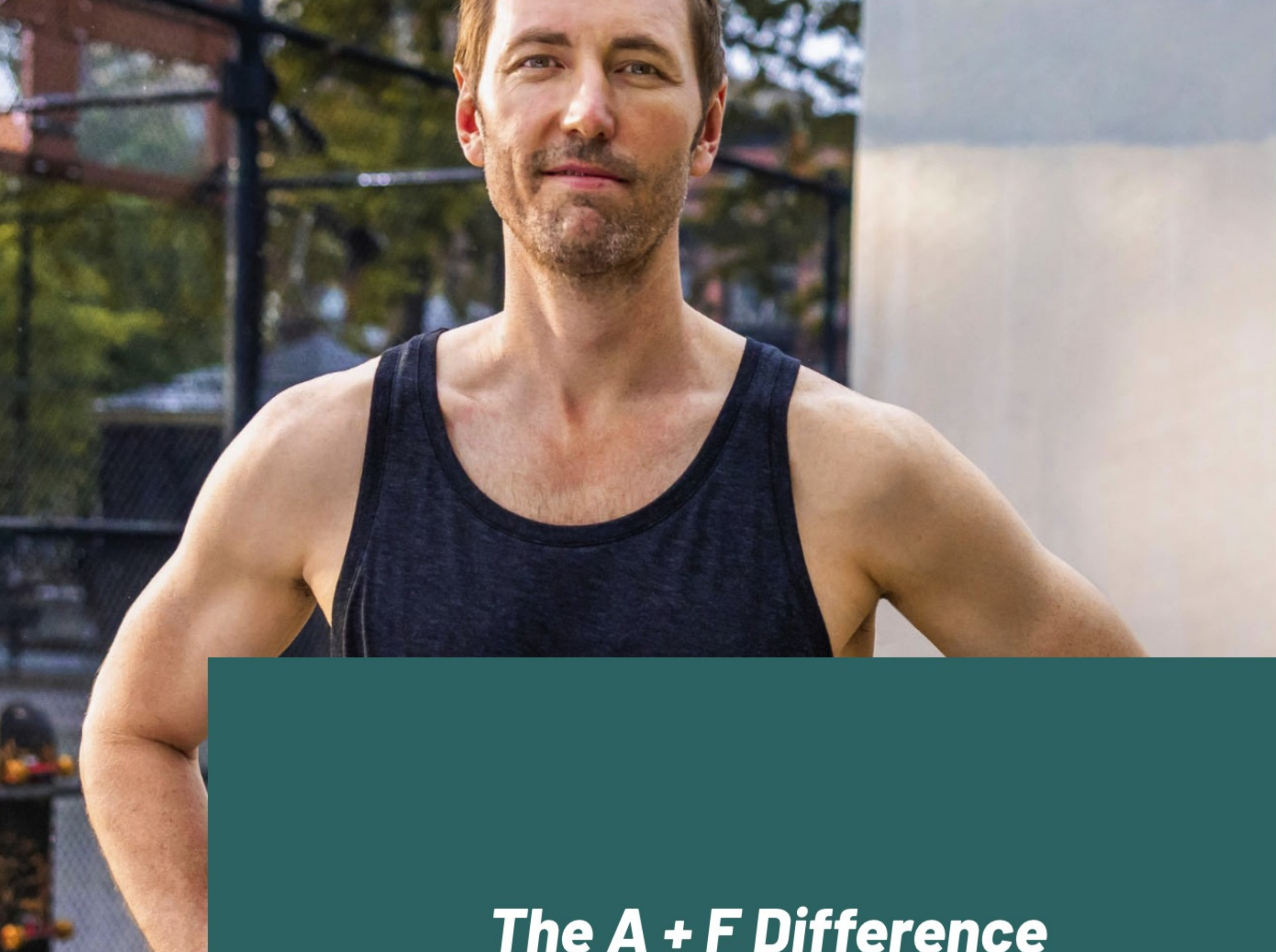
Happily Retired

Lahey Clinic

Department of Rheumatology

Presented to the Lexington Computer and Technology Group, May 8, 2024

This talk is unfortunately not being supported by any drug company



# How BIMZELX<sup>®</sup> works differently

## The A + F Difference

Most biologic treatments target just one of the proteins, like IL-17A, believed to drive the inflammation that causes plaque psoriasis.

**BIMZELX targets two proteins.**

TARGETS  BLOCKS

**IL-17A**

+

**IL-17F**

### IMPORTANT SAFETY INFORMATION:

BIMZELX is a medicine that affects your immune system and may increase your risk of serious side effects, including suicidal thoughts and behavior, serious infections including tuberculosis, liver problems, and

BIMZELX<sup>®</sup> is a prescription medicine used to treat adults with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or treatment using ultraviolet light alone or with pills (phototherapy).

# Goals of Talk

- To review the **history of inflammation**
- To talk about **basic cell biology**
- To introduce the concept of **Interleukins**
- To show the **relevance** of inflammation today



# News Hour TV Ads

# News Hour TV Ads

Skyrizi

News Hour TV Ads  
Modern “Anti Inflammatory” Medications

Skyrizi

Humira

Rinvoq

These

News Hour TV Ads  
Modern “Anti Inflammatory” Medications  
Skyrizi  
Humira  
Rinvoq

*Understanding a bit about inflammation is important because these medications  
all work by modifying the body’s  
Inflammatory Response.*



## Aulus Cornelius Celsus ~50 AD

*Notae vero inflammationis sunt quatuor: rubor et tumor cum calore et dolore”*

The signs of inflammation are four: redness and swelling with heat, and pain.

*Functio laesa*, loss of function.

(The fifth sign of inflammation was later added by Galen ~ 180 AD)

## Inflammed Knee



*rubor et tumor cum calore et dolore*

The Gingerbread Man goes to the rheumatologist...



The Gingerbread Man goes to the rheumatologist...

Does ice block inflammation?



# Inflammation $\neq$ Infection

Infection is an **invasion** of the body from an outside source.

Inflammation is the **body's response** to any invasion or insult.

# Inflammation $\neq$ Infection

Infection is an invasion of the body by a living source.

An Organism:

Virus, Bacteria, Parasite, Fungus

# Inflammation $\neq$ Infection

Infection is an invasion of the body from an outside source.

Virus, Bacteria, Parasite, Fungus

Inflammation is the body's response to **any** invasion or insult.

Invasive organism

Foreign Body

Wound or Injury

Tetanus Shot

Perceived Internal Foreign Source

# Inflammation $\neq$ Infection

The inflammatory response tries to kill the invader.

But, what if we cannot kill the invader?

Can you kill a crystal?

Can you kill a tetanus shot?

How can you kill altered DNA?



# Inflammation $\neq$ Infection

If we cannot kill the invader  
we try to block its effect by increasing inflammation.

The host often become sicker.

We then have to fight our own inflammatory response to return to  
health!

# Pop Quiz # 1

- In Roman times, other than battle axes and chariot accidents, what was the most common cause of inflammation?
  - A Rheumatoid Arthritis
  - B Tuberculosis
  - C Gout

**How do we Block Inflammation?**

## How to Block Inflammation

Three Breakthroughs in the Understanding of Inflammation:

- 1.) Aspirin
- 2.) NSAIDS
- 3.) Interleukins

ASPIRIN

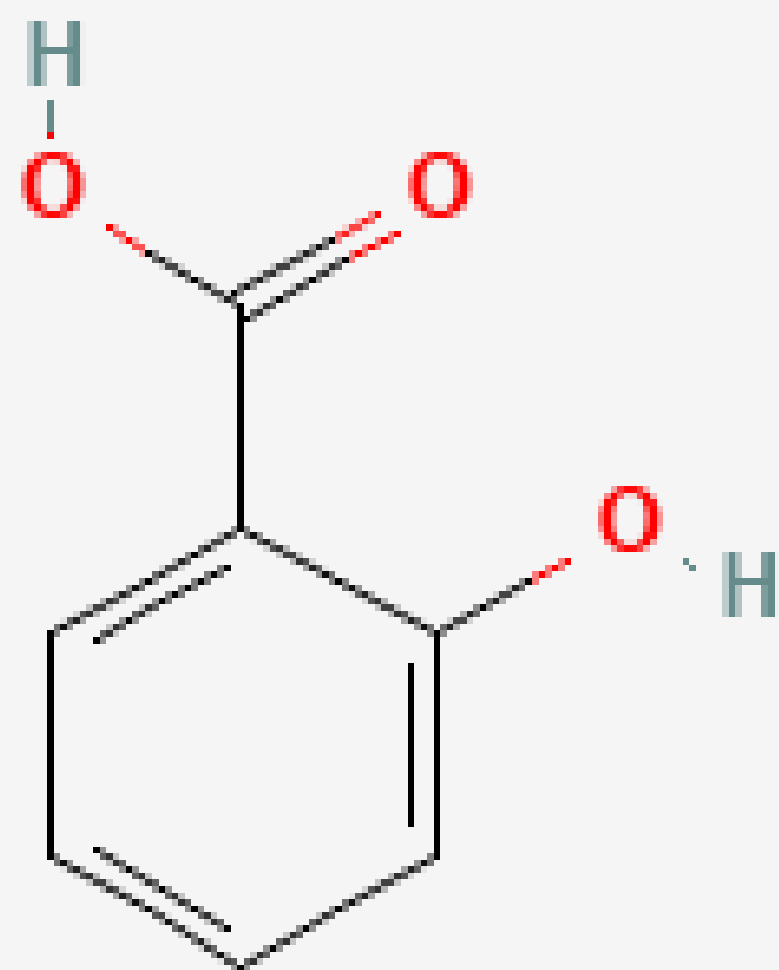
ASPIRIN



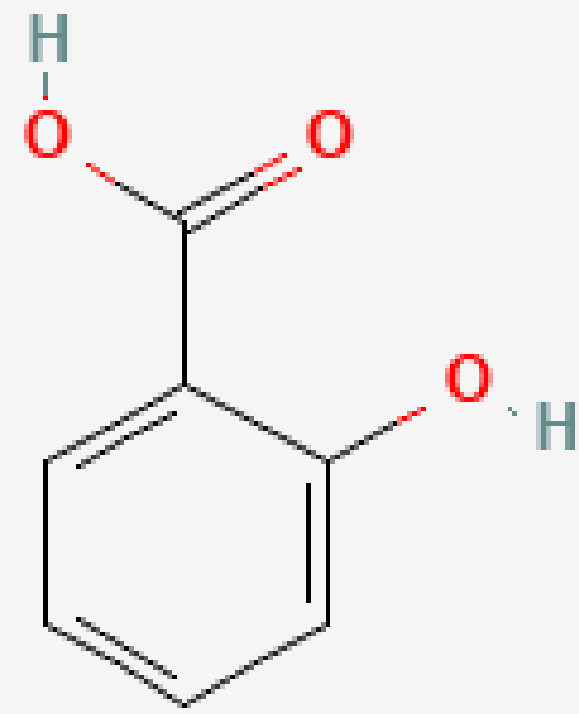
**Felix Hoffmann**  
**1897**

ASPIRIN

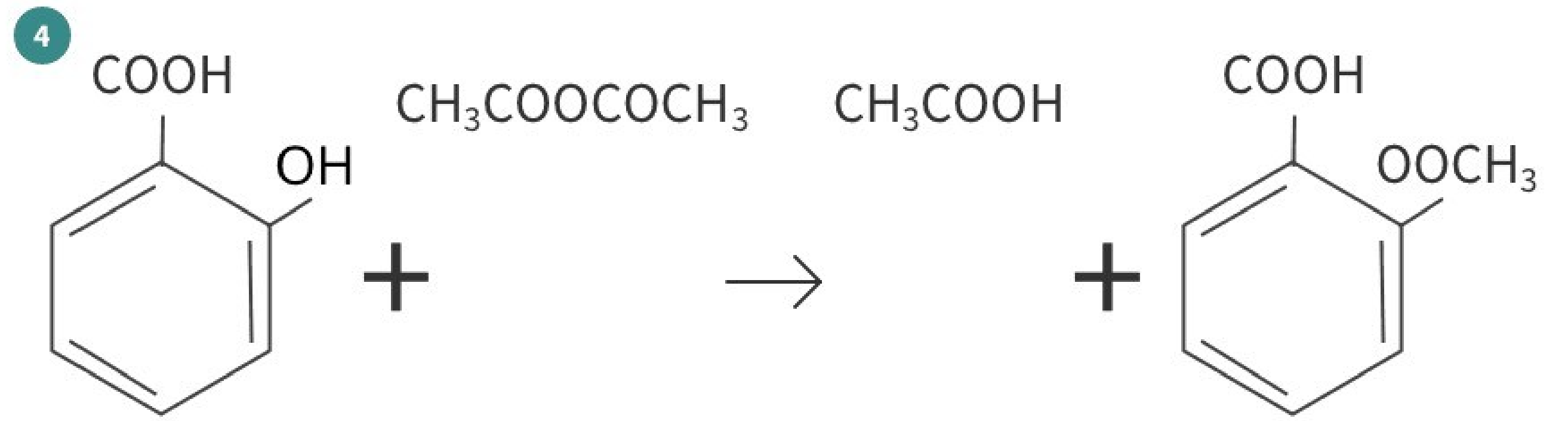
Hoffman's Father



**Salicylic Acid**



**Salicylic Acid**



Salicylic Acid

Acetic Anhydride

Acetic Acid

Aspirin

**Acetylsalicylic Acid**



# Acetylsalicylic Acid

A spirin  
Aspirin

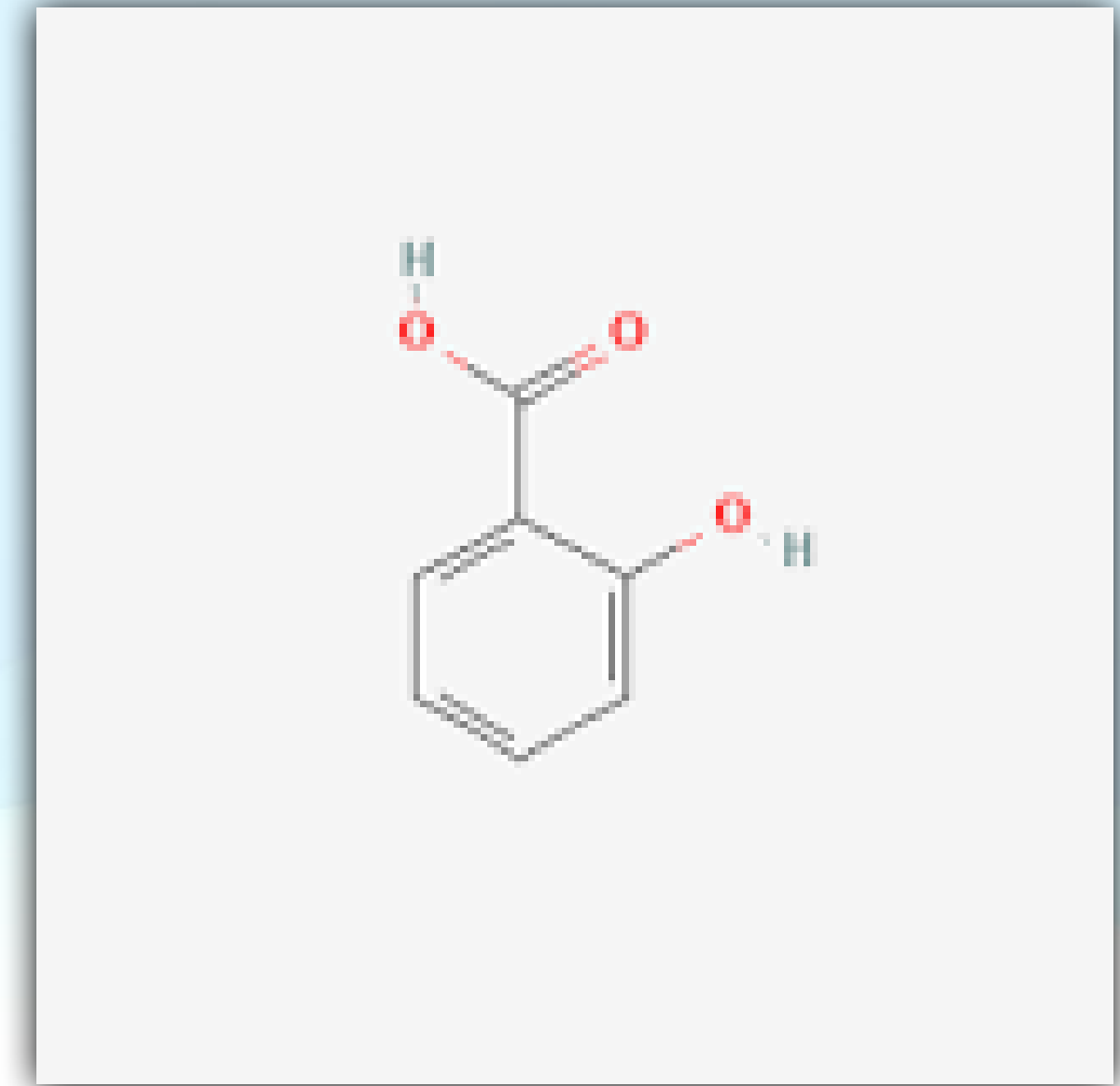


Aspirin, from the **A** for **acetyl** and the **spirin** from **Spirea**, the genus name for shrubs that are an alternative source of salicylic acid.





Salicylic acid chemically is a benzene ring with both a phenol (HO) group and a carboxylic acid (COOH) group.



Other scientists had focused on the carboxylic acid group.

Dr Hoffman acetylated the phenol group and produce pure stable acetylsalicylic acid (ASA) for the first time.

After the discovery Professor Heinrich Dreser, Head of the Pharmacology Institute at Bayer, tested it on himself before successful humans trials.



**Felix Hoffmann in 1897**  
**Acetylsalicylic Acid**

**?**

ASPIRIN



**Felix Hoffmann in 1897**

**Acetylsalicylic Acid**

**Dihydromorphine  
(Dilaudid)**



## Felix Hoffmann in 1897

Acetylsalicylic Acid

**Diacetylmorphine**

Heroin (Heroisch)

ups are bound to some organic molecules, the resulting compounds are **more easily absorbed** and **more rapidly eliminated**. The resulting compounds have **increased serum levels** and can cross the blood-brain more rapidly than the parent compound for a given dose.

ASPIRIN has 2 basic effects:

- 1.) Blocks inflammation
- 2.) Causes stomach irritation.

How does ASA actually work to block inflammation and why does it cause stomach pain and bleeding?

1971

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**JR Vane**  
1971  
“Eureka Moment”





**JR Vane**  
1971  
“Eureka Moment”

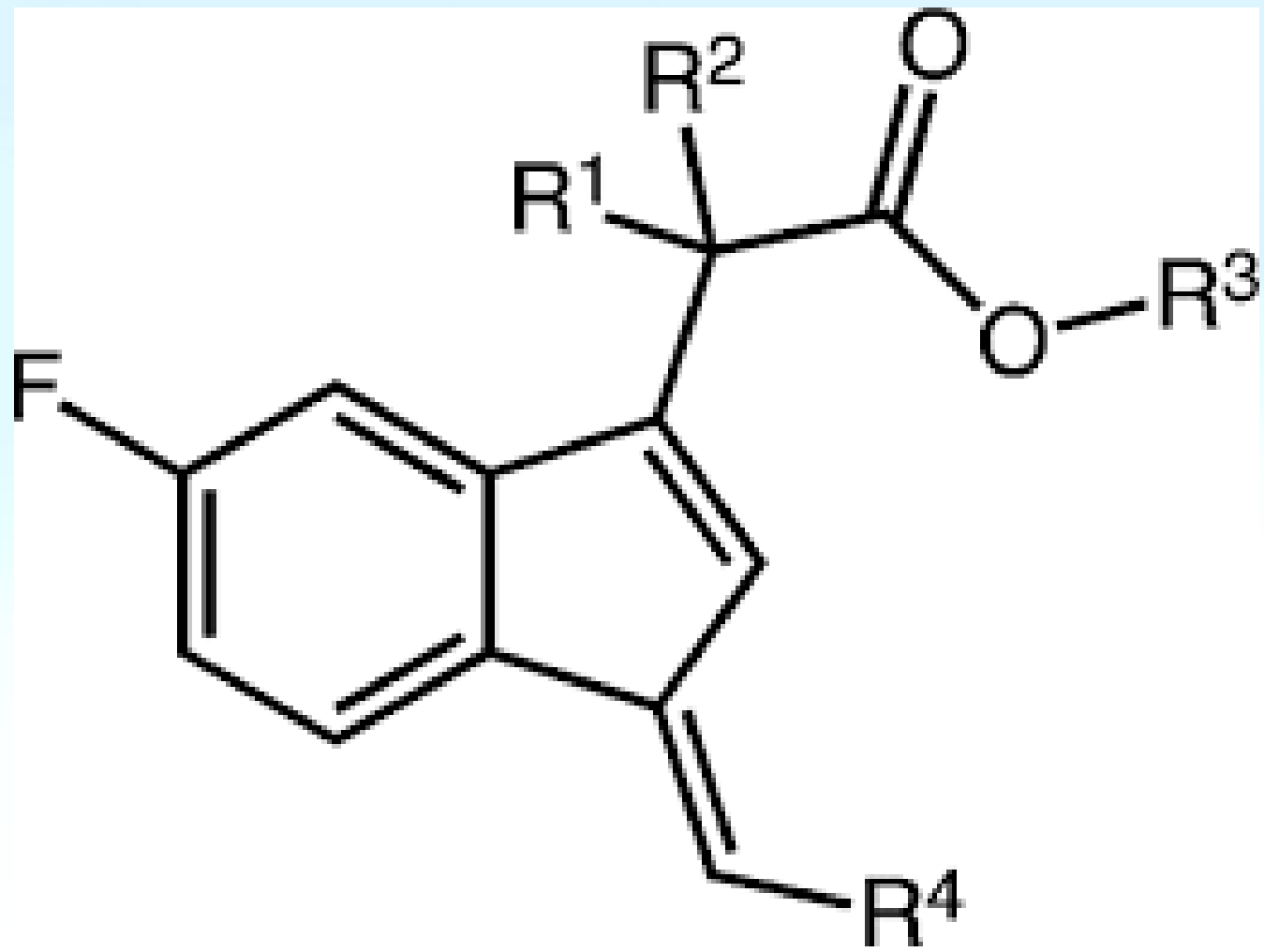
**Prostaglandins**



**1971** John Vane discovered that **aspirin** inhibits the synthesis of prostaglandins by blocking the enzyme cyclooxygenase.

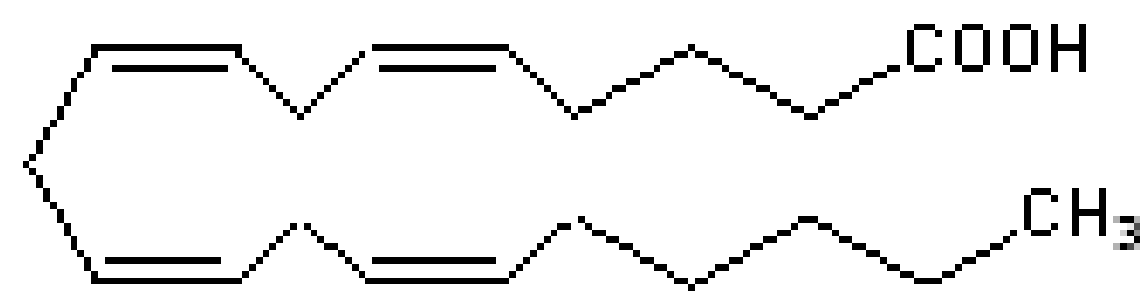
**1984** He was knighted by the Queen for his discovery.

**NSAIDS**

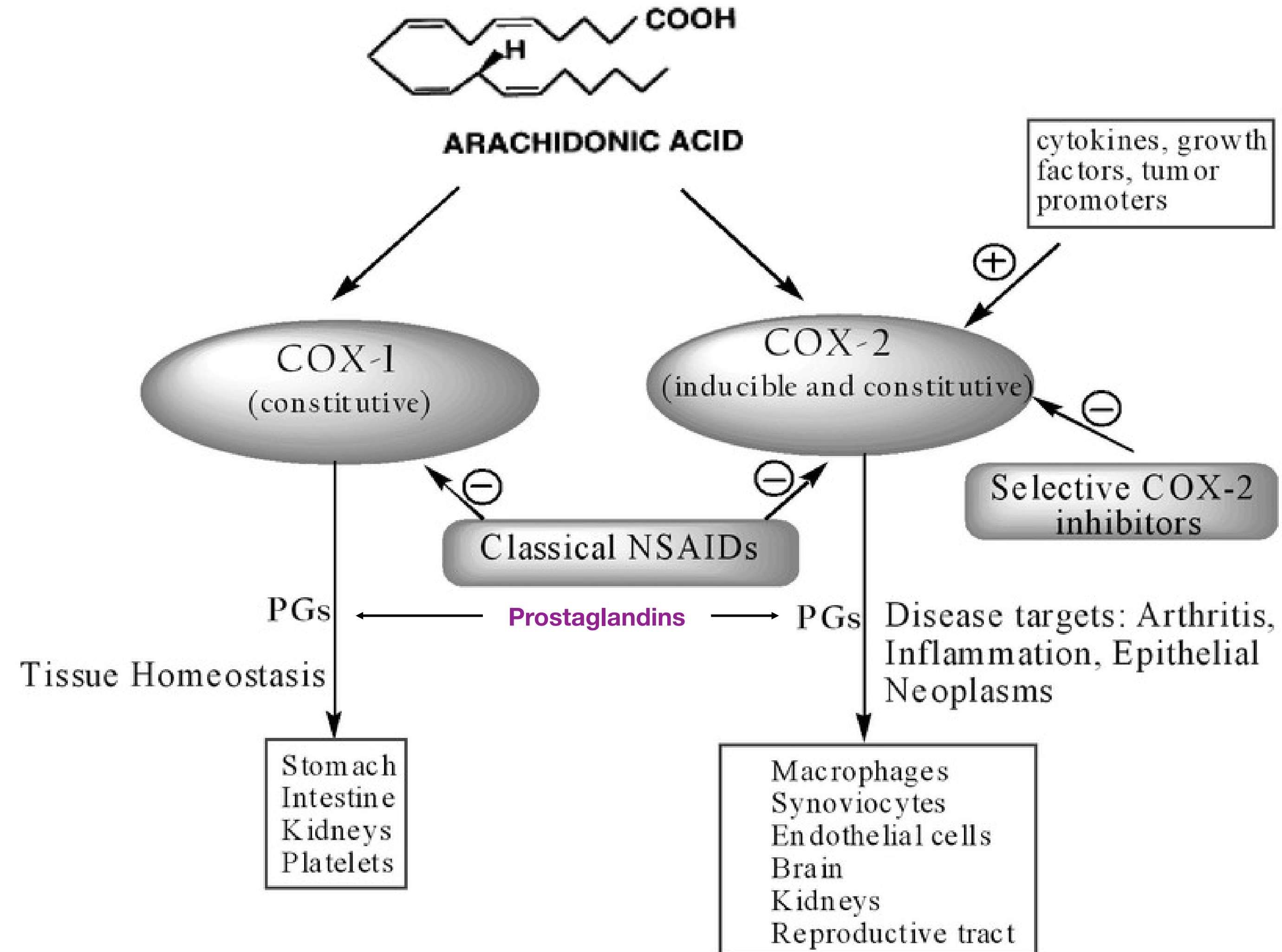


**Cyclo-Oxygenase**

## NSAIDS



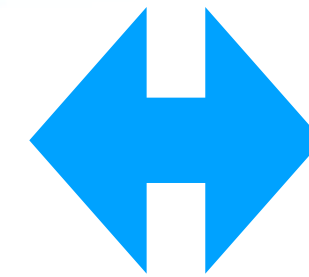
**Arachidonic Acid**



**COX - 1 Inh**  
Isoleucine

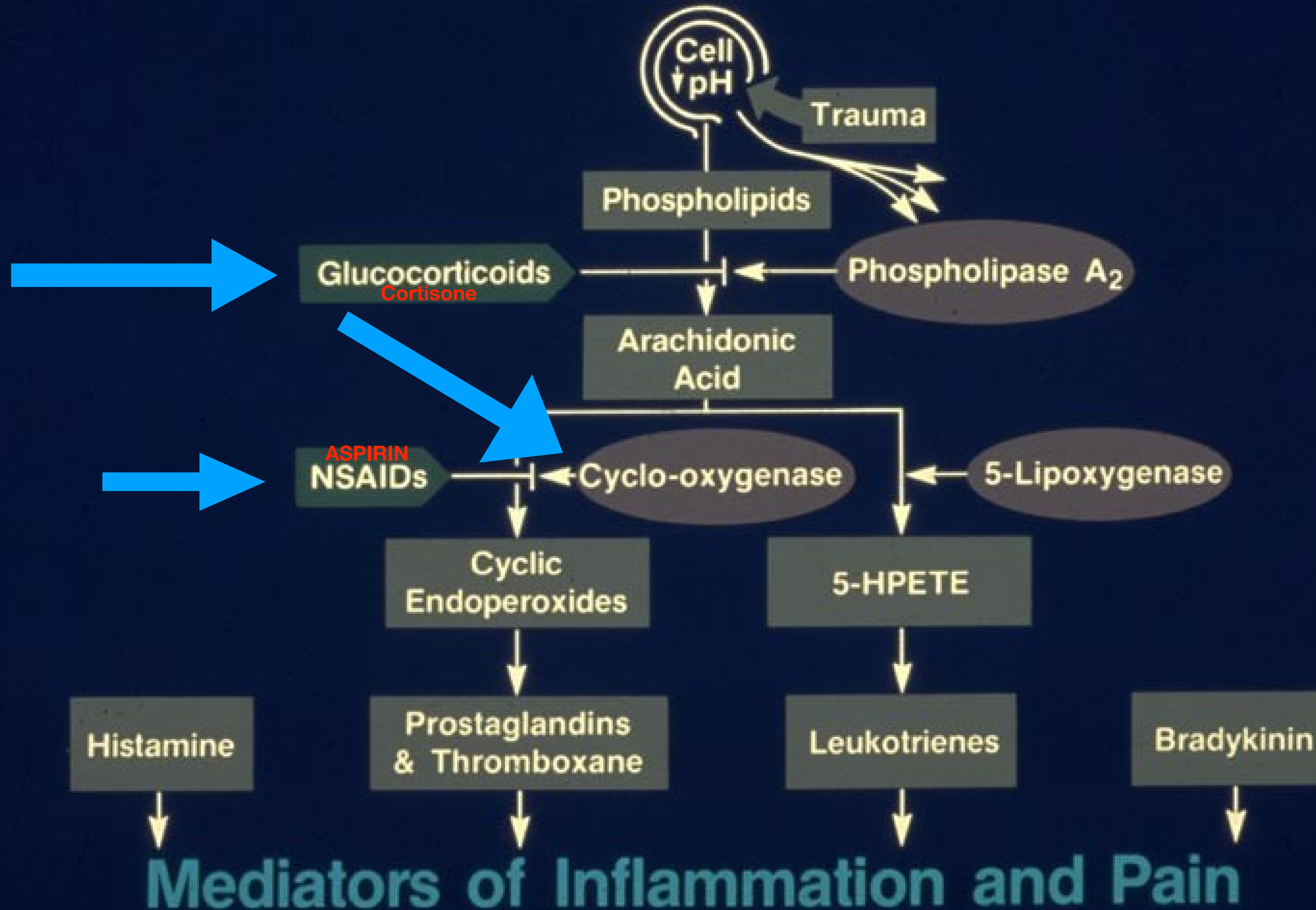
**COX - 2 Inh**  
Valine

**GI Toxicity**



**CV Toxicity**

# The Arachidonic Cascade



# NSAIDS



Salicylates	NSAIDS All since 1972				
Salicylic Acid	Motrin	Feldene	Arcoxia		
Choline Salicylate	Nalfon	Mobic	Acular	Toradol	
Aspirin 1897	Naproxen	Etodolac	Ocufen	Vioxx	
Indocin 1961	Tolectin	Celebrex	Diflunisal		
	Clinoril	Prexige	Ketoprofen		
	Meclomen	ANSAID	Relafen		
	Nambumetone	Daypro			

All NSAIDS and Salicylates work by ~ blocking the cyclo-oxygenase enzymes.

# NSAIDS

- Two classes: COX-1 Inhibitors and Cox-2 Inhibitors
  - Most NSAIDS have mixed effects
  - Some are more selective than others.

**Table 1. NSAID Selectivity**

More COX-1 Selective	Nonselective	5-50-fold COX-2 selective <sup>a</sup>	>50-fold COX-2 selective <sup>a</sup>
Ketorolac (Acular) <b>Toradol</b> Flurbiprofen (Ocufen) Ketoprofen (Generic) Indomethacin (Indocin) Aspirin (Generic) Naproxen (Aleve) Tolmetin (Generic) Piroxicam (Feldene) Meclofenamate (Generic)	Ibuprofen (Advil, Motrin) Fenoprofen <sup>b</sup> (Nalfon) Sodium salicylate (Generic) Diflunisal (Generic)	Sulindac (Clinoril) Diclofenac (Cambia) Celecoxib (Celebrex) Meloxicam <sup>c</sup> (Mobic) Etodolac (Generic)	Etoricoxib <sup>d</sup> (Arcoxia) Lumiracoxib <sup>d</sup> (Prexige)
<b>Increased gastrointestinal effects</b> ←————→ <b>Increased cardiovascular effects</b>			
<sup>a</sup> Listed in order of increasing COX-2 selectivity <sup>b</sup> Equipotent for COX-1 and COX-2 selectivity <sup>c</sup> At higher doses, COX-2 selectivity decreases and COX-1 inhibition increases <sup>5</sup> <sup>d</sup> Not yet approved by the FDA			

COX, cyclooxygenase; FDA, Food and Drug Administration; NSAID, non-steroidal anti-inflammatory drug

- Classes
- Administration
- Adverse Reactions
- Common Brand Names
- Dea Class
- Description
- Dosage And Indications
- Dosing Considerations
- Drug Interactions
- How Supplied
- Maximum Dosage
- Mechanism Of Action
- Pharmacokinetics
- Pregnancy And Lactation

# Colcrys Colchicine

## Classes



## Administration



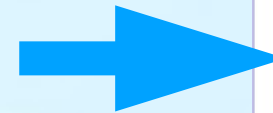
## Adverse Reactions



## Common Brand Names



## Dea Class



Safari File Edit View History Bookmarks Develop Window Help

1 Cloud Mail www.bostonglobe.com Sport Distance...ng, Hiking... Login | Charles Schwab Saint Petersburg to Rēzekne Apple My hoopla - hoopla Apple Bing Google Yahoo

Drug Summary

**PDR**  
by ConnectiveRx®

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## Toradol

### Boxed Warning

**Limit duration of use**

Systemic use of ketorolac is only indicated for the short-term management of moderately severe acute pain that requires analgesia at the opioid level. The oral tablets are only indicated as continuation treatment after IV or IM administration, if necessary. Limit duration of use so the total combined duration of oral and parenteral ketorolac does not exceed 5 days because of the increased risk of serious adverse events. Also, doses higher than recommended will not increase efficacy but will increase the risk of developing serious adverse events; the maximum recommended daily oral dose is significantly lower than the maximum daily parenteral dose. Ketorolac ophthalmic drops may be administered for up to 4 days after corneal refractive surgery.

**Bleeding, surgery**

Like all NSAIDs, ketorolac may increase the potential for hematological complications. Systemic formulations are contraindicated for use as a prophylactic analgesic before major surgery and contraindicated for use during surgery when hemostasis is critical; cautious use of the ophthalmic solution is advised with ocular surgery. Perioperative use has been associated with postoperative hematomas and other events. Postoperative use when hemostasis is critical is not recommended. Bleeding after a single IV or IM dose in pediatric patients was greater after tonsillectomy vs. other procedures. Ketorolac, in all forms, should be used with caution in patients with known bleeding tendencies and in patients who are receiving other medications that may prolong bleeding time (e.g., anticoagulant therapy) as such patients have an increased risk of bleeding complications. There

- Classes
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1970's



# Blood Basics

- Blood Components
  - Red Blood Cells
  - White Cells: PMNL, **Lymphocytes**, Monocytes
  - Clotting Cells: Platelets
  - Other Cells: Stem Cells, Dendritic Cells





# Immune System Basics à la 1970s Lymphocytes

- T-Cells      Innate Immunity
- B-Cells      Acquired Immunity
- Nul-Cells    Non Committed Cells
- Perhaps Tolerance Cells

# Parts of the Immune System

**Innate**

**Acquired**

**Non-Specific**

**Antigen Specific**

**Immediate Response  
T-Cell Responses**

**Lag Phase  
B-Cell Responses**

**No Memory**

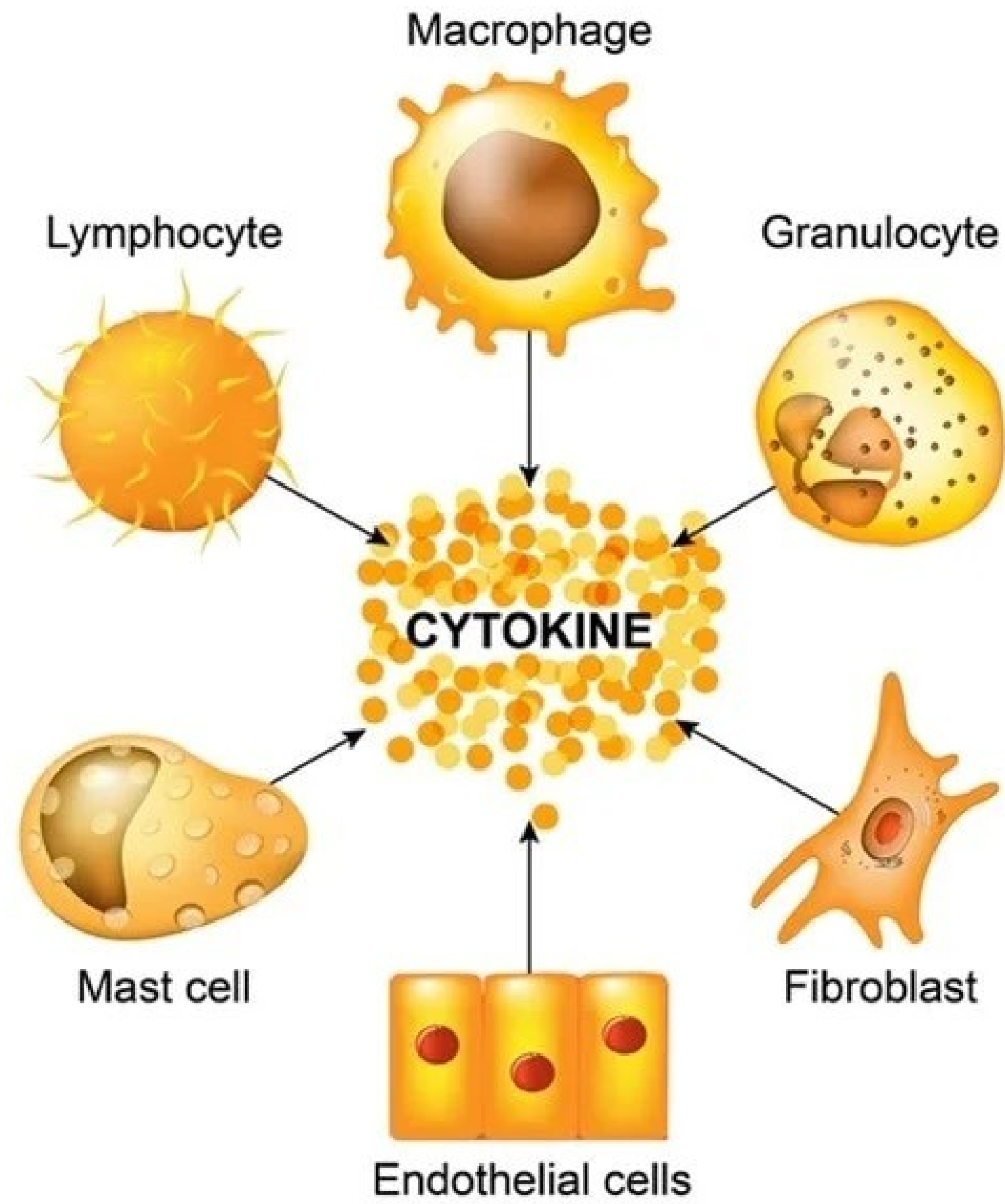
**Memory T cells**

**Ubiquitous**

**Only Higher Vertebrates**

IMMUNE  
SYSTEM

Science  
ABC



*Cytokines. Image Credit: Designua / Shutterstock*

- Cytokines CYTO + KINOS ~ cell substances which are signal proteins
- Interleukins INTER + LEUKOCYTE ~ communicate between white cells

# INTERLEUKINS

Named in 1979

Interleukins are one type of cytokines.

They are proteins **created immediately** in response to membrane stimulation.  
That stimulation **signals mRNA** to produce other Interleukins.

Interleukins have **redundant purposes** including effecting other interleukin synthesis.  
They act at remote sites to modulate inflammation.

We recognize the **symptoms** they produce as either **signs of inflammation**  
or the **pattern of a discrete illness**.

# **INTERLEUKINS**

Named in 1979

**Interleukins are one type of cytokines.**

**They are proteins created immediately in response to membrane stimulation.  
That stimulation signals mRNA to produce the specific Interleukin.**

**Interleukins have redundant purposes including effecting other interleukin synthesis.  
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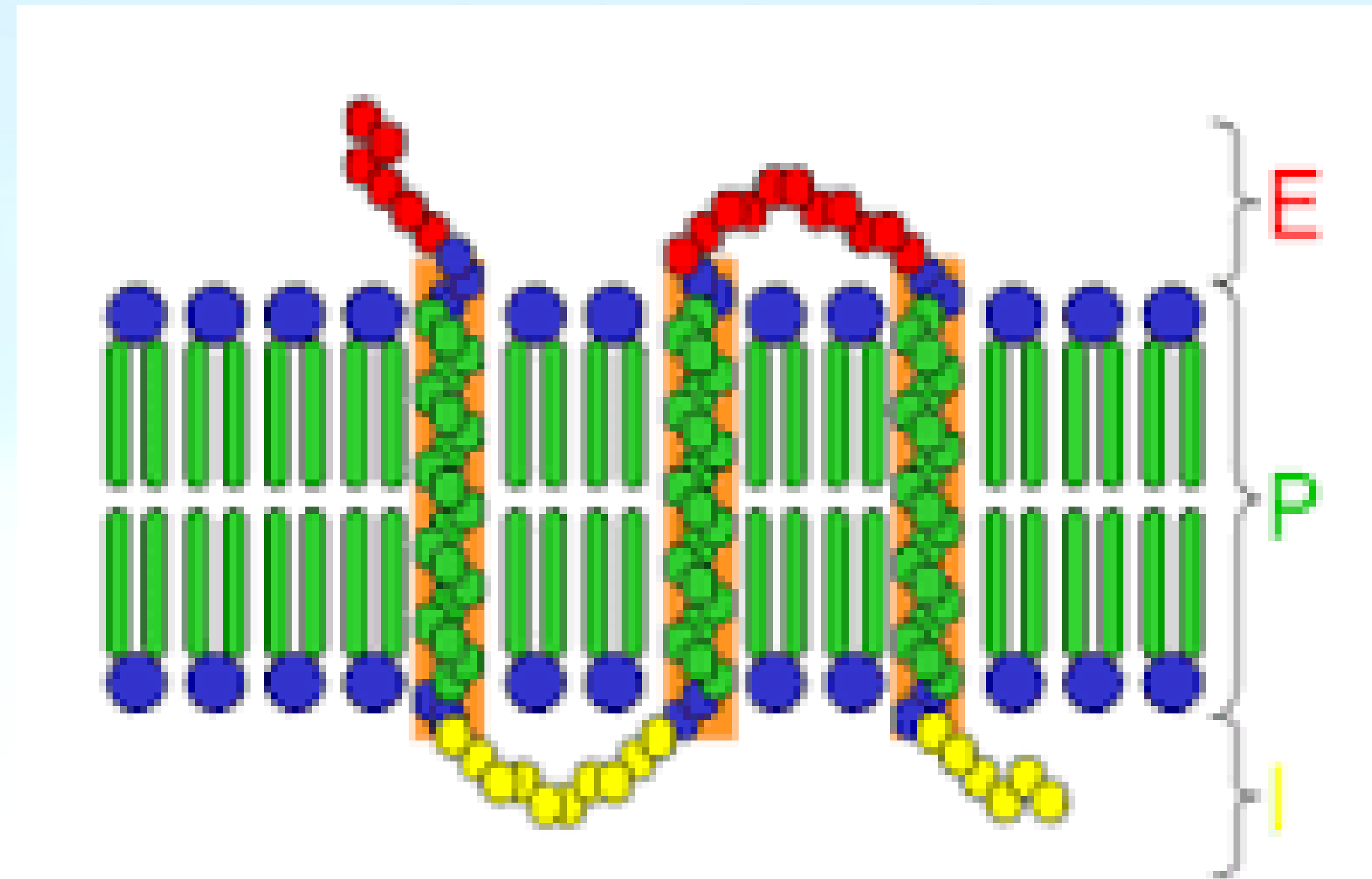
**We recognize the symptoms they produce as either signs of inflammation  
or the pattern of a discrete illness.**

**How to Interleukins actually work?**

# Cell Biology

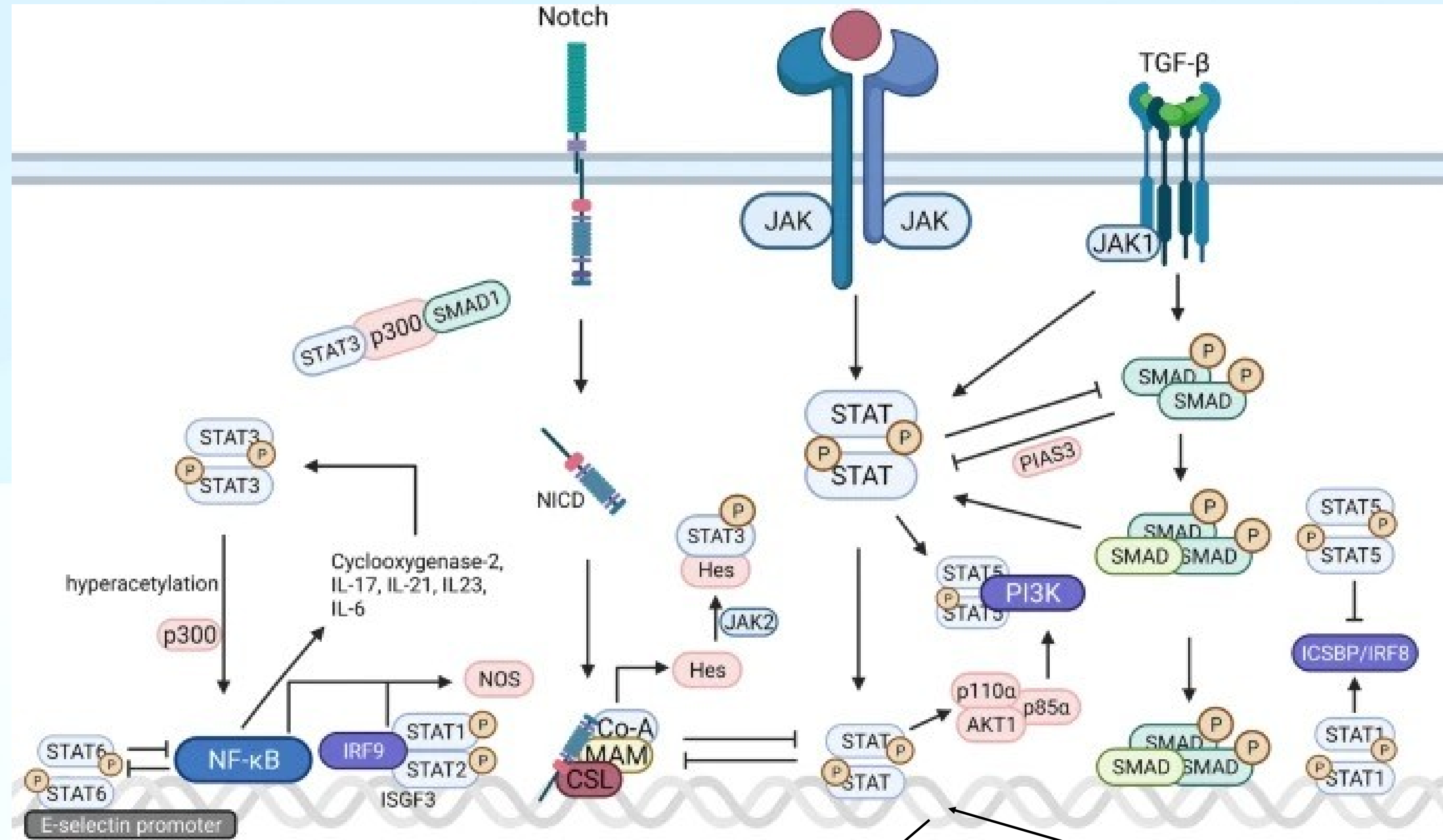
~2000

## Cell Surface Receptors Wiki





# Cell Surface Receptors



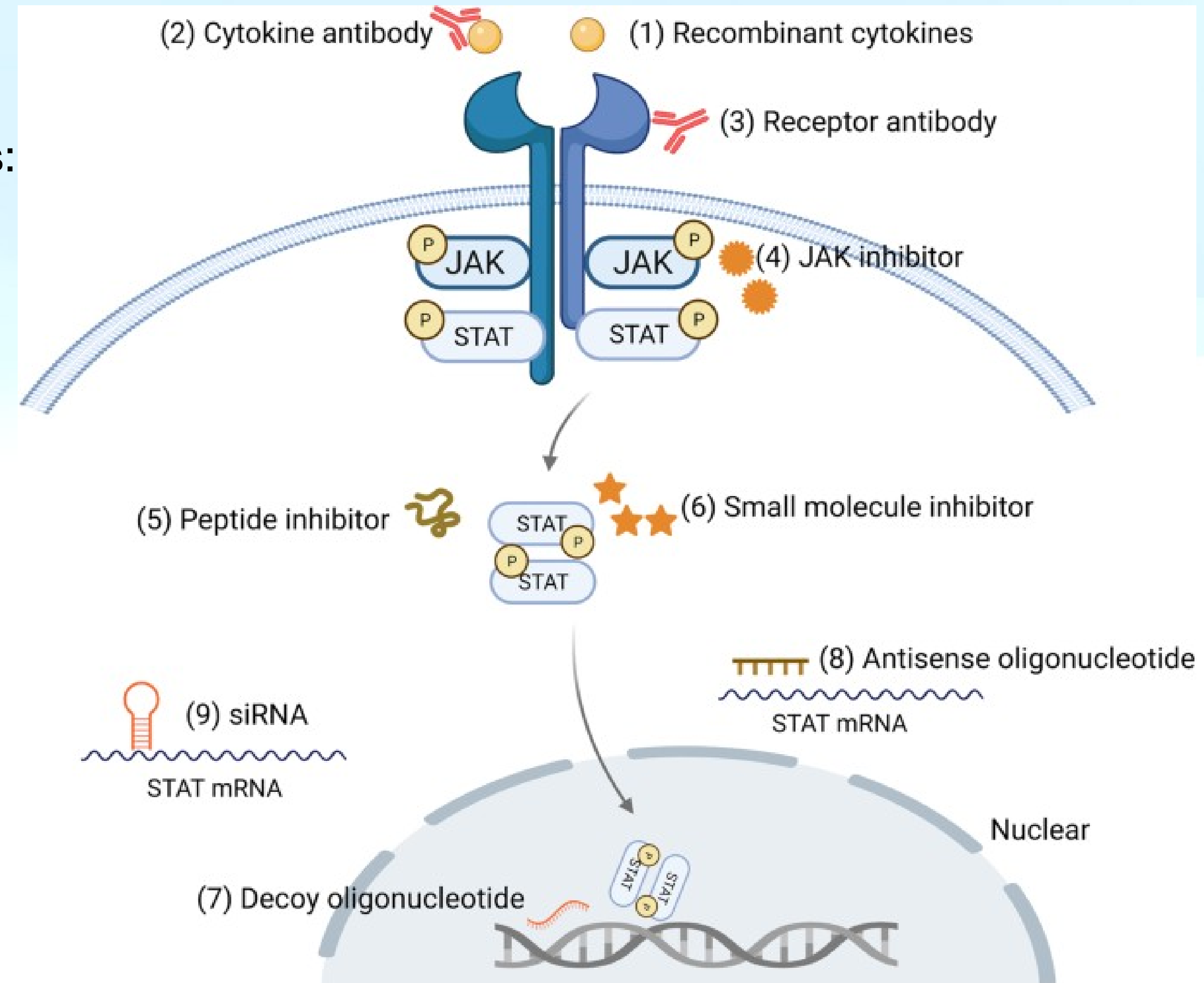
Specific Interleukin

m-rna

# JAK/STAT Receptor

The JAK-STAT system consists of three main components:

- (1) a receptor (blue) which penetrates the cell membrane;
- (2) Janus kinase (JAK) protein which is bound to the receptor, and;
- (3) Signal Transducer and Activator of Transcription (STAT) protein which carries the signal into the nucleus and DNA or RNA for binding.

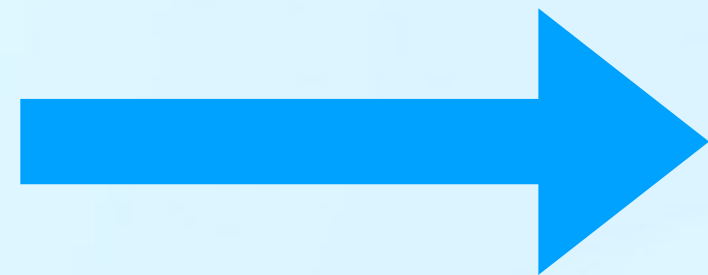


# JAK Inhibitors

- Janus Kinase Inhibitors **RINVOQ**
- Pop Quiz # 2
  - Who was Janus?

# JAK Inhibitors

- Janus Kinase Inhibitors
- Who was Janus?
  - In Roman mythology, Janus was the god of beginnings, gates, transitions, duality, and doorways. He is usually depicted as having two faces. The month of January is named for Janus, the beginning month of the year.



Interleukin (cytokine)	Source	Target cell	Effect
IL-1	Macrophage, lymphocytes, endothelium, fibroblasts, astrocytes	T-cells, B-cells, macrophage, endothelium, tissue cells	Lymphocyte activation, leukocyte-endothelial adhesion, fever, regulates sleep
IL-2	T-cells	T-cells	T-cell growth factor
IL-3	T-cells	Bone marrow cells	Stimulates bone marrow growth
IL-4	T-cells	B- and T-cells	B-cell growth factor
IL-5	T-cells	B-cells	B-cell growth factor
IL-6	T- and B-cells, macrophages, fibroblasts	B-cells and hepatocytes	B-cell differentiation and synthesis of acute phase reactants
IL-7	Lymphocytes	B- and T-cells	Stimulates proliferation of immature cells
IL-8	T-cells, macrophages	Granulocytes, endothelium	Stimulates the activity of neutrophils, acts as chemotaxin, inhibitor of endothelial cell-leukocyte adhesion
IL-9	T-cells	T-cell	T-cell and mast cell growth enhancement
IL-10	T-cells	Macrophage	Suppresses the development of T-cell subpopulations (TH <sub>1</sub> ) by inhibition of macrophage IL-12 production
IL-11	Bone marrow stromal cells	Hepatocyte	Induces synthesis of acute phase proteins
IL-12	Macrophage	T-cells	Enhances the B-cells expression of IFN- $\gamma$ during T-cell activation; also stimulates a lymphocyte subpopulation (NK cells)

Modulates the Immune Response

# What Is Interleukin 17?

Interleukin 17 is a potent **inflammatory** cytokine produced by activated memory T cells.

It **recruits neutrophils**, and is involved in both the innate and adaptive immune systems.

It causes inflammation in **RA, allergies, asthma, psoriasis, and Crohn's Disease.**

It also plays a role in tumorigenesis (initial formation of a tumor) and transplant rejection.

**IL-17 family may represent an ancient signaling system throughout vertebrate evolution.**

**IL-17 is a family of related proteins.**

# What Is Interleukin 17?

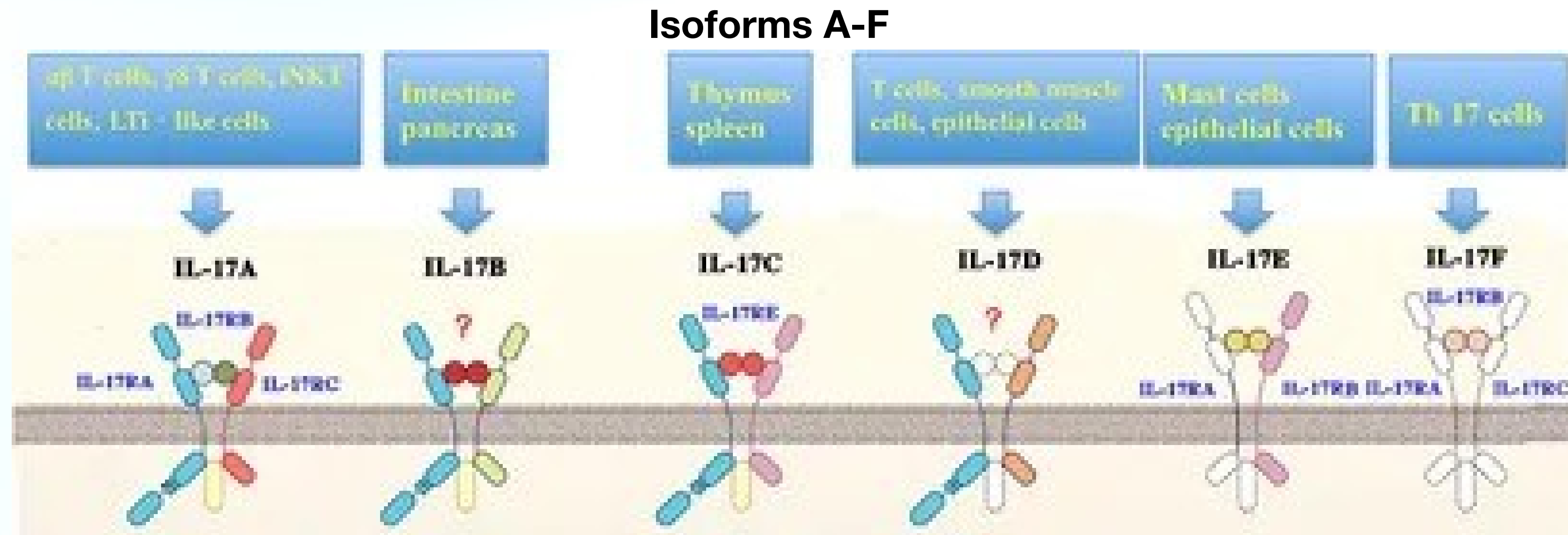
Interleukin 17 is a potent pro-inflammatory cytokine produced by activated memory T cells.

It recruits neutrophils, and is involved in both the innate and adaptive immune systems.

It causes inflammation in rheumatoid arthritis, allergies, asthma, psoriasis, Crohn's Disease, cancer development, and transplant rejection.

It is present as a signaling system throughout vertebrate kingdom.

IL-17 isoforms are produced in **at least 6 discrete cell types**:





# How BIMZELX<sup>®</sup> works differently

## The A + F Difference

Most biologic treatments target just one of the proteins, like IL-17A, believed to drive the inflammation that causes plaque psoriasis.

**BIMZELX targets two proteins.**

TARGETS  BLOCKS

**IL-17A**

+

**IL-17F**

### IMPORTANT SAFETY INFORMATION:

BIMZELX is a medicine that affects your immune system and may increase your risk of serious side effects, including suicidal thoughts and behavior, serious infections including tuberculosis, liver problems, and inflammatory bowel disease.

BIMZELX<sup>®</sup> is a prescription medicine used to treat adults with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or treatment using ultraviolet light alone or with pills (phototherapy).



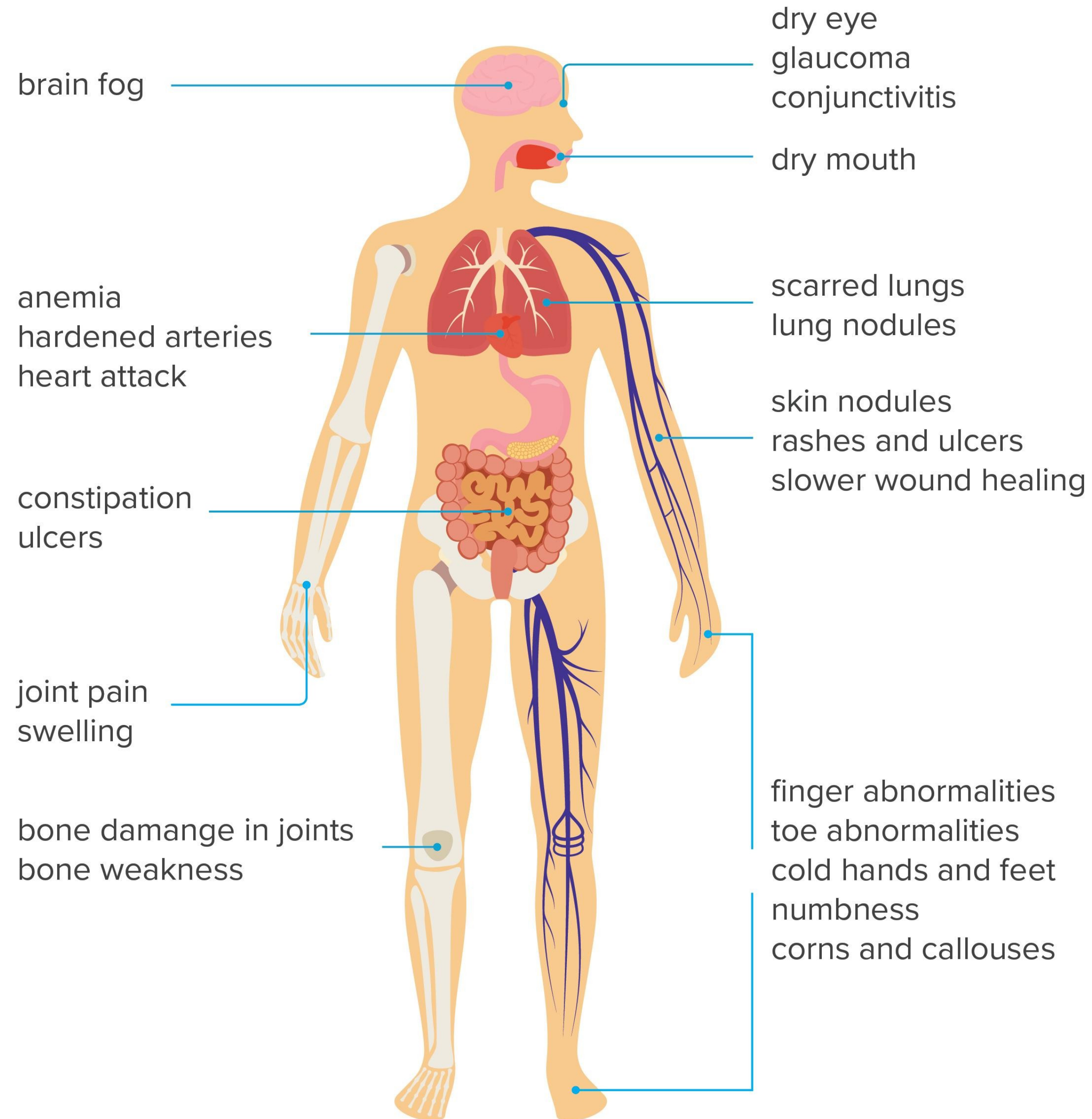


**Disease or Multi-System Disease?**

# Effects on the Body

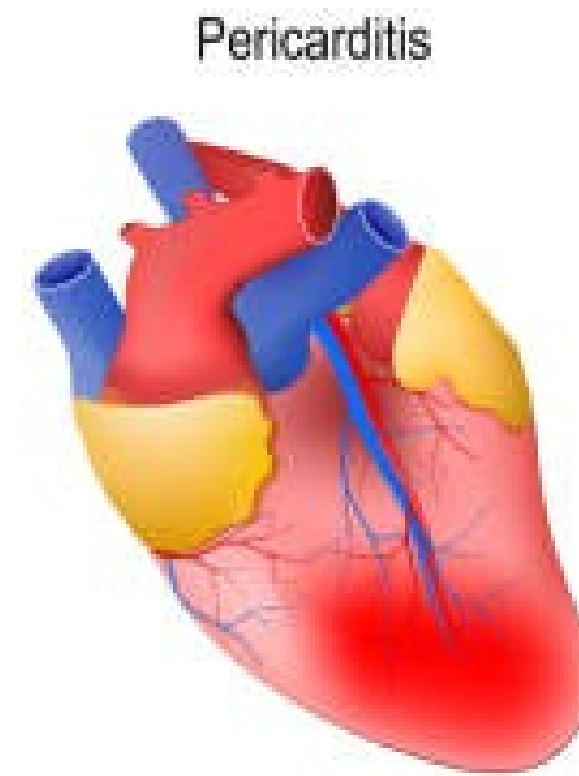
## Rheumatoid Arthritis

### Disease or Multi-System Disease?



# Systemic lupus erythematosus

## Disease or Multi-System Disease?



JOINT PAIN  
(small joints of the hand  
and wrist usually affected)



# DISEASE

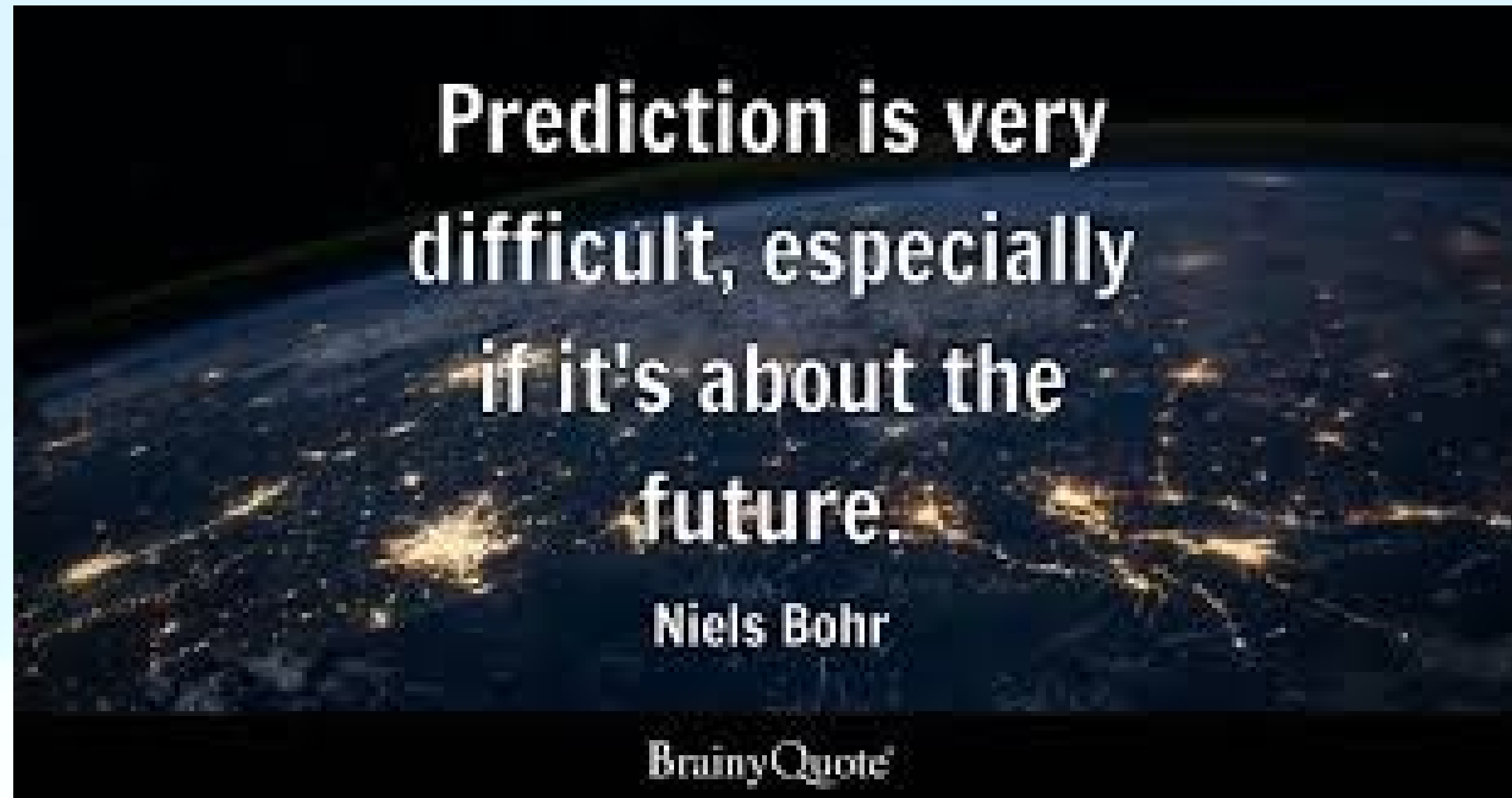
## SYMPTOM COMPLEX Based Treatment

Illness	Marker	Possible Treatment
Strep Throat Rheumatic Fever	Positive Throat Culture	Penicillin
Rheumatoid Arthritis	Rheumatoid factor	Humira
Crohn's Disease	Barium Enema	Skyrizi
Systemic Lupus	Anti-DNA Antibody	Trial and Error

# MULTI SYSTEM DISEASE

## INFLAMMATION Based Treatment

Illness	Marker	Possible Treatment
Strep Throat Rheumatic Fever	Positive Throat Culture Many Interleukins	Penicillin
Rheumatoid Arthritis	IL-1, IL-6 TNF-Alpha	Actemra Humira
Rheumatoid Arthritis	Membrane JAK/STAT Receptor	Rinvoq
Crohn's Disease	Elevated IL-6, IL-23 Other Interleukins	Skyrizi
Psoriatic Arthritis	Elevated IL-17A & IL-17F	Bimzelx
Systemic Lupus	Multiple Interleukins	IL-2



### **My Prediction:**

**Inflammation based treatment will become more common as well as more confusing.**

# SOME TV ADVERTISED INTERLEUKIN ACTIVE MEDICATIONS

TRADE NAME	GENERIC NAME	ACTION	INDICATIONS		TRADE NAME	GENERIC NAME	ACTION	INDICATIONS
Enbrel	Etanercept	TNFa Blockade	RA, AS, PsA		Skirizi	Risankizumab	Interleukin 23a Blocking Agent	Crohn's PsA
Humira	Adalimumab	TNFa Blockade	RA, AS, PsA		Tremfya	Guselkumab	Interleukin 23a Blocking Agent (p19 subunit)	PsA
Remicade	Infliximab	TNFa Blockade	RA		Otezla	Apremilast	PDE4 Depletor	PsA
Cimzia	Certolizumab	TNFa Blockade	RA		Cyclosporine	Cyclosporin A	450 Cytochrome Selective Inhibitor	RA
Symponi	Golimumab	TNFa Blockade	RA		Xeljanz	Tofacitinib	JAK/STAT Pathways	RA, PsA, AS, UC
Orencia	Abatacept	T cell Co-stimulator blocking agents	RA		Olumiant	Baricitinib	JAK/STAT Pathways	RA, Alopecia
Rituxan	Rituximab	B cell Depleting Agent	RA		Kesimpta	Ofatumumab	CD20An B cell Binding	MS
Kineret	Anakinra	Interleukin -1 Receptor Antagonist	RA		Verzenio	Abemaciclib	Enzyme Inhibitor	Breast cancer
Actemra	Tocilizumab	Interleukin -6 Receptor Antagonist	RA, PMR, JIA, COVID		Omvoh	mirikizumab	Interleukin 23 Blocking Agent	UC
Kevzara	Sarilumab	Interleukin -6 Receptor Antagonist	RA, PMR, XeljansCOVID		<b>BIMZELX</b>	bimekizumab-bkzx	<b>Interleukin 17A and 17F Blocking Agent</b>	Psa
Talz	Ixekizumab	Interleukin 17A Blocking Agent	RA					
Cosentyx	Secukinumab	Interleukin 17A Blocking Agent	PsA, AS					
Stelara	Ustekinumab	Interleukin 12 and 23 Blocking Agent	Crohns, Psoriasis, PsA					

# Goals of Talk

- To review the history of inflammation ~ Aspirin, NSAIDS, Interleukins
- To talk about basic cell biology ~ Cell membranes and mRNA signaling
- To introduce the concept of Interleukins ~ The worker bees
- To show the relevance of inflammation today ~ Direct patient advertising



Novice Monk

*Doctor Monk makes  
a monastery call...*



"IT'S VERY INFLAMED. WHY DON'T YOU  
TAKE A VOW OF SILENCE FOR A FEW DAYS?"

*Thank you,  
Jerry Harris*



**Thank you!**

**Questions and Comments**

# INFLAMMATION

A Primer

May 8, 2024



# The Arachidonic Cascade

