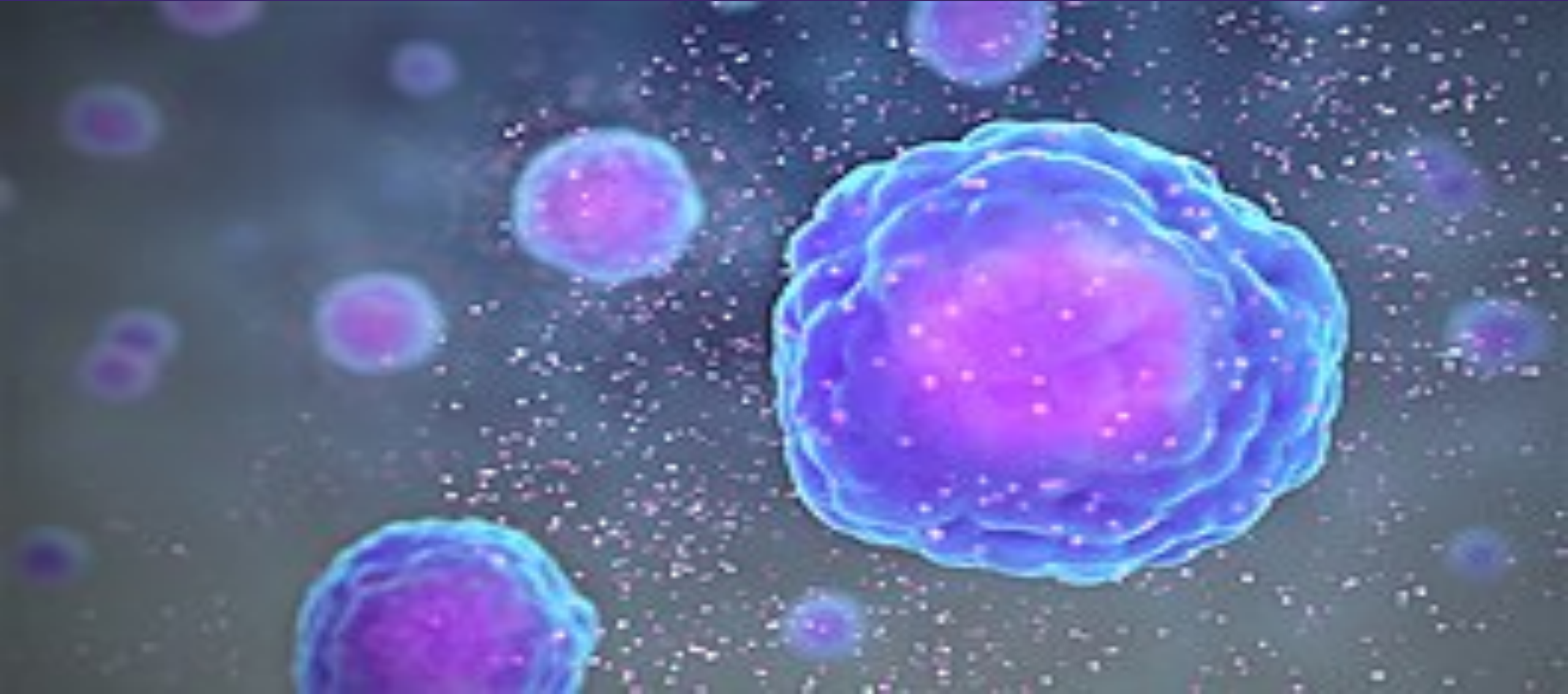


Cytokines

In Pain and More

Threat vs Safety



Cytokine

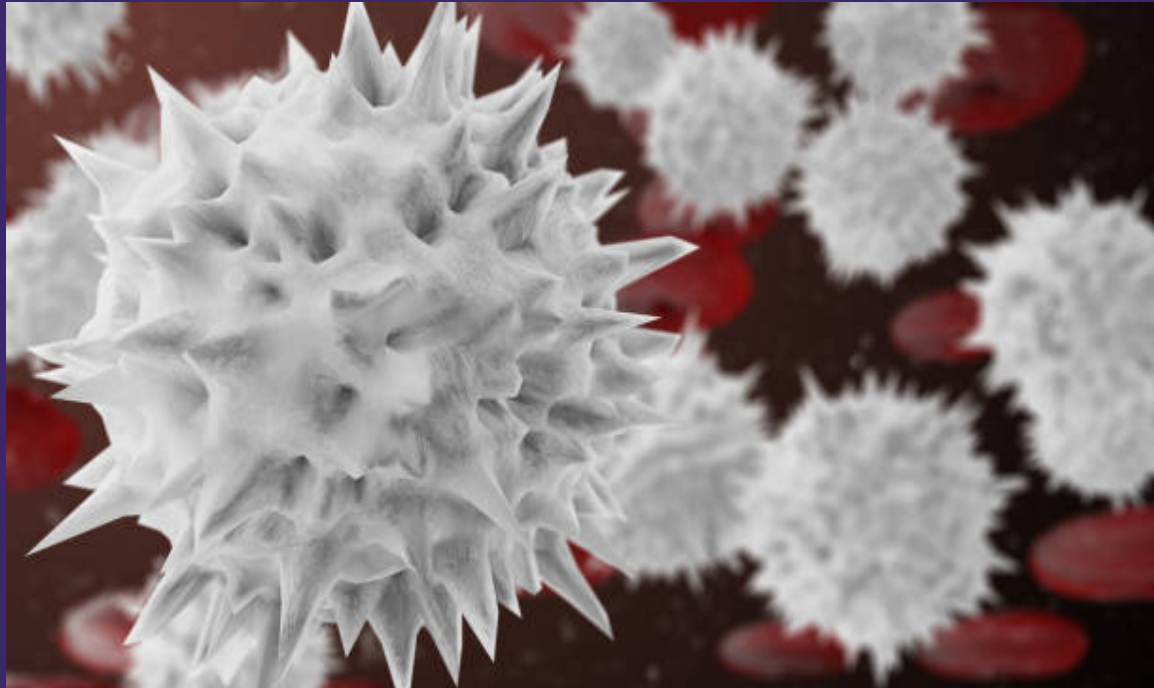
Small Protein Signaler

Cyto

- Cell (cavity)

Kine

- Movement (kinesis)



Bacteria and Archaea

Inter cellular Communication

3.5 Billion Years Ago

- Cell-Cell Signaling System
- Original system of communication
- Small proteins $\sim$ = 10-20 aa
- Cell membrane receptors
- Quorum sensing
- Asocial vs Prosocial
 - Low metabolism and isolation
 - High metabolism, swarming, colonization, specialization, division of labor, sharing of public goods, tend to each other

Cytokines

Intercellular Communication

750 Million Years Ago

- Cell-Cell Signaling System
- Advanced system of communication
- Small-Proteins $\sim$ = 100-200 amino acids
- Cell membrane receptors
- Quorum sensing - monocytes
- Autocrine – secrete and bind to same cell
- Paracrine – secrete and bind to another local cell
- Endocrine – secrete and bind to another distant cell
- Asocial and Prosocial?

Types of Cytokines

Large family with families of protein signalers

- *Monokines* - 1969
- *Lymphokines* - 1969
- Interferons – 1957
- Chemokines – 1966
- Interleukins - 1977
- Tissue growth factors – 1981
- Tumor necrosis factors – 1985 “Cachectin”

Threat vs Safety

Threat Cytokines

- IL1
- IL2
- IL6
- IL17
- TNFs

Pro Inflammation

Pro Nociception

Catabolic

Safety Cytokines

- IL4
- IL10
- IL11
- IL13
- TGFs

Anti Inflammation

Anti Nociception

Anabolic

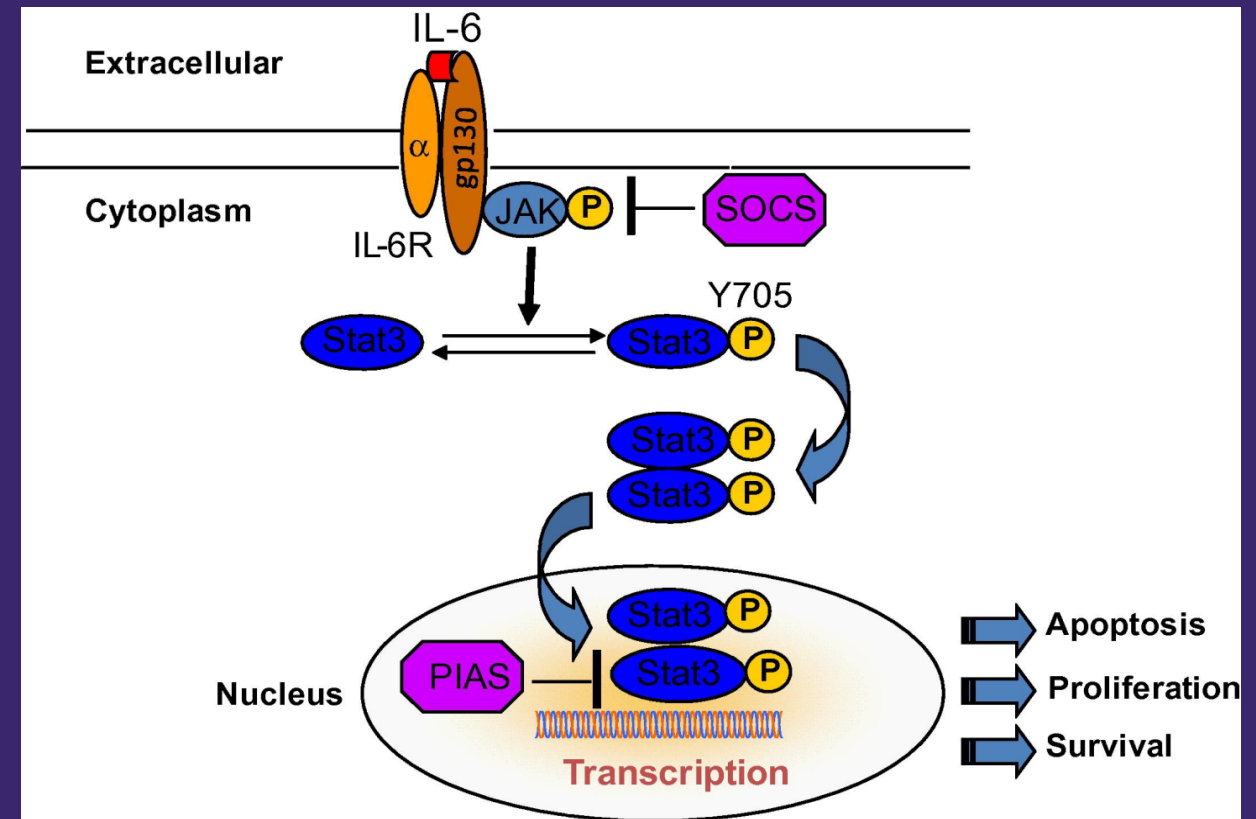
Production of Cytokines

- **Leukocytes** (Monocytes, Macrophages, Mast Cells, T lymphocytes, B lymphocytes)
- Endotheliocytes
- Epitheliocytes
- Fociocytes
- Gliocytes
- Neurons
- Osteocytes
- Adipocytes

Connective Tissues +

Pleiotropic Network

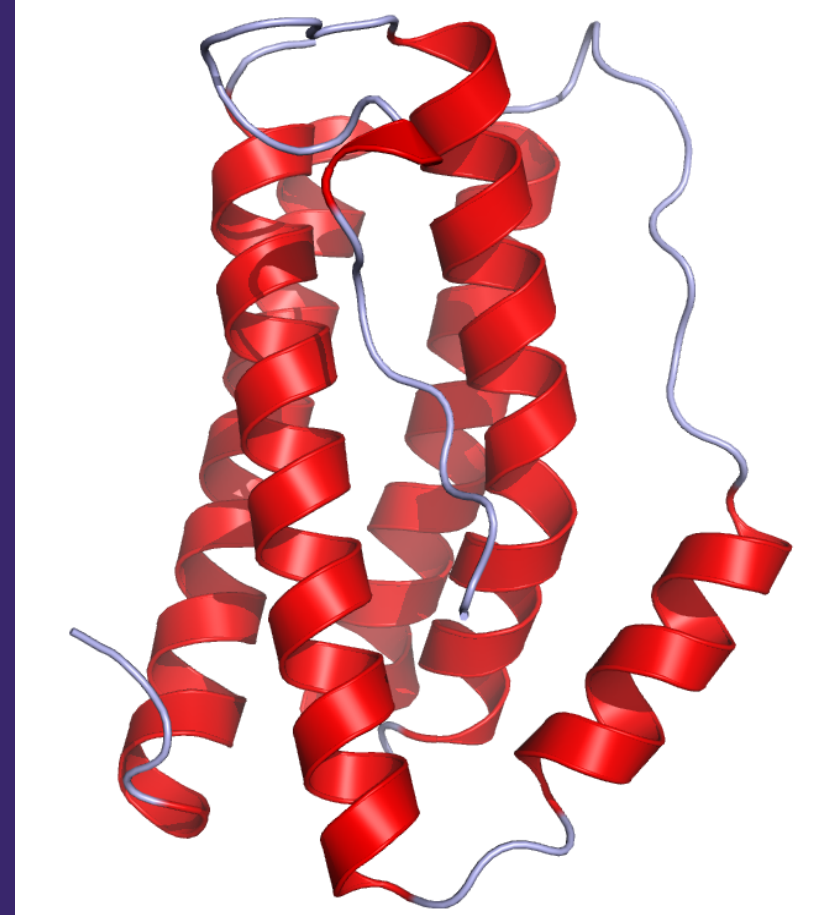
- A lot of them
- Cell membrane receptors
 - concentration
 - high affinity and low affinity
 - density
 - location/tissue type
- Influence other cell's membrane receptors
 - sensitivities
- Induce cytoplasmic activity
- Induce nuclear activity
- Affect their own and others transcription



IL6

Acute

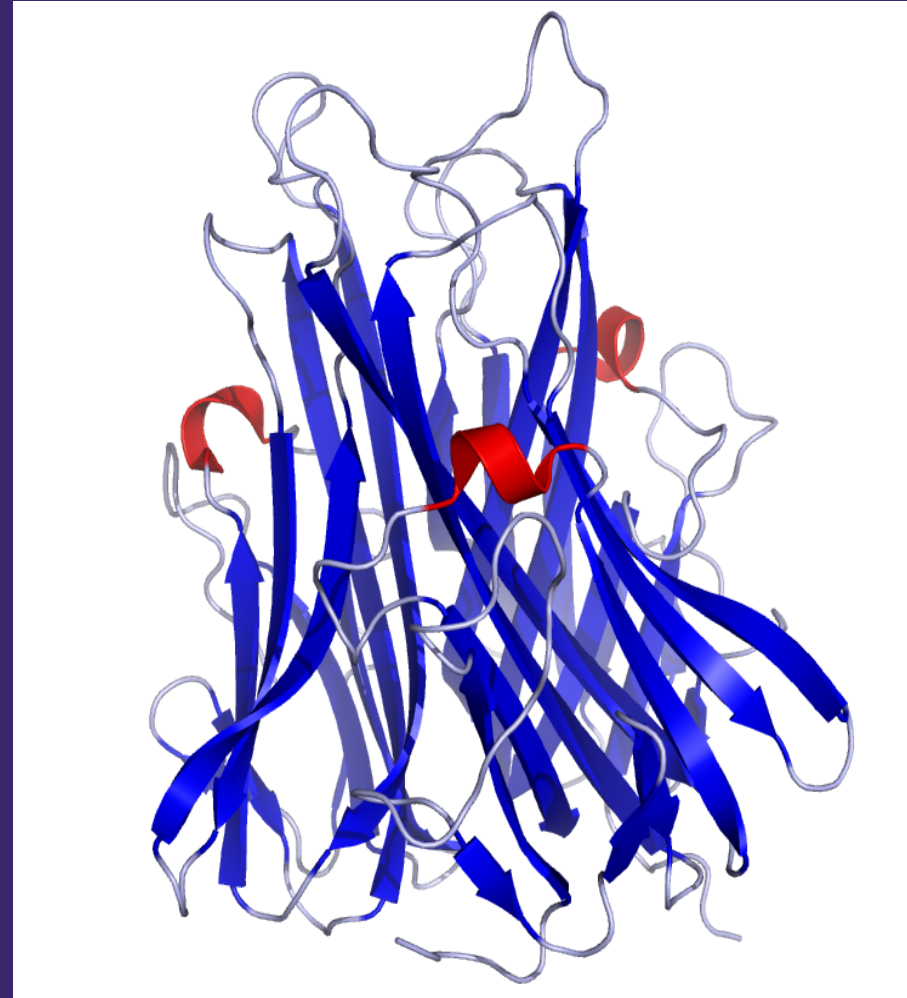
- Fever
- Fatigue
- Malaise
- Anorexia
- GI stasis
- Shock
- Hyperalgesia
- Allodynia
- Headache
- Arthralgia
- Myalgia



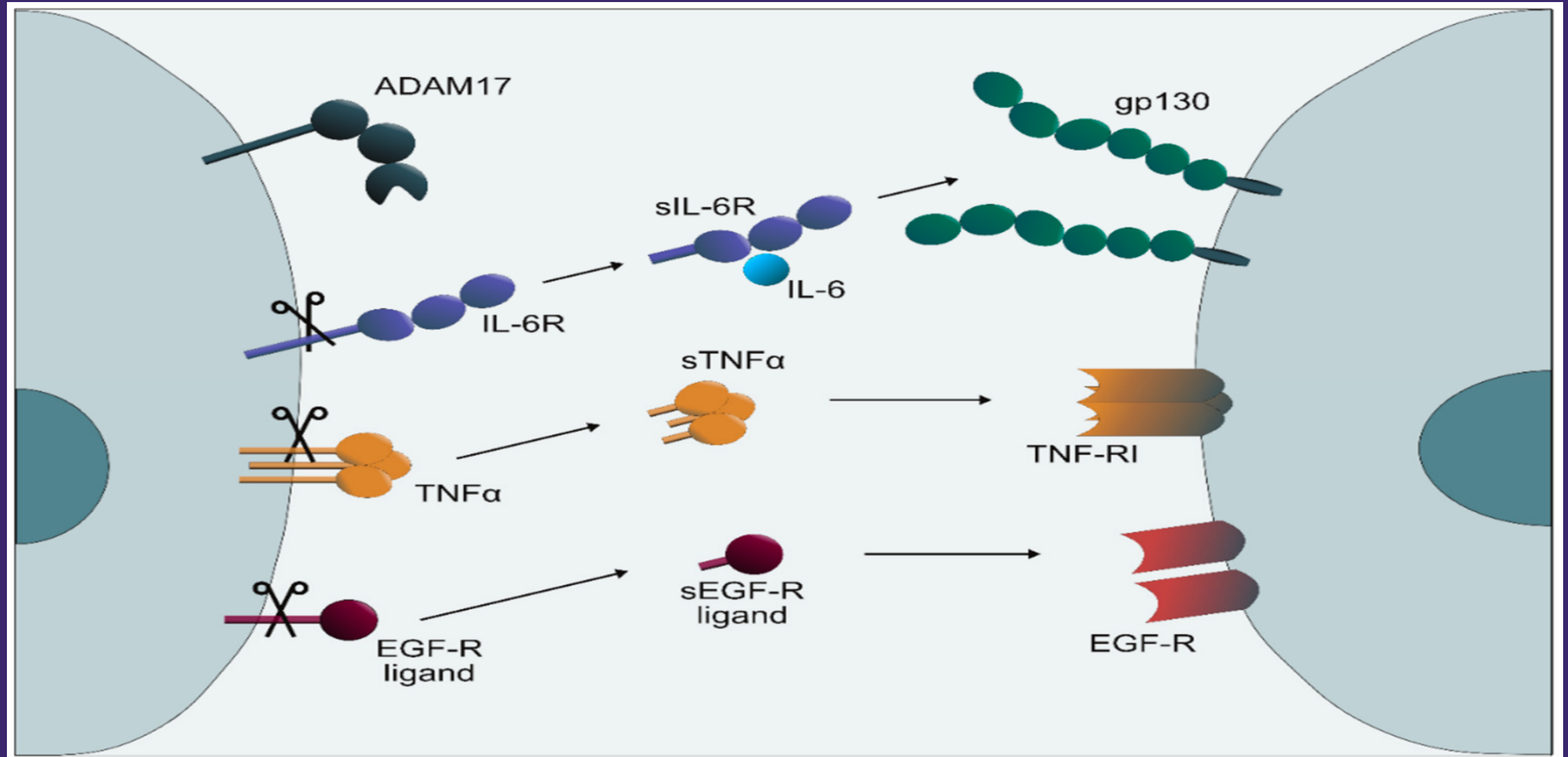
TNF alpha

Acute

- Fever
- Fatigue
- Malaise
- Anorexia
- GI stasis
- Shock
- Hyperalgesia
- Allodynia
- Headache
- Arthralgia
- Myalgia



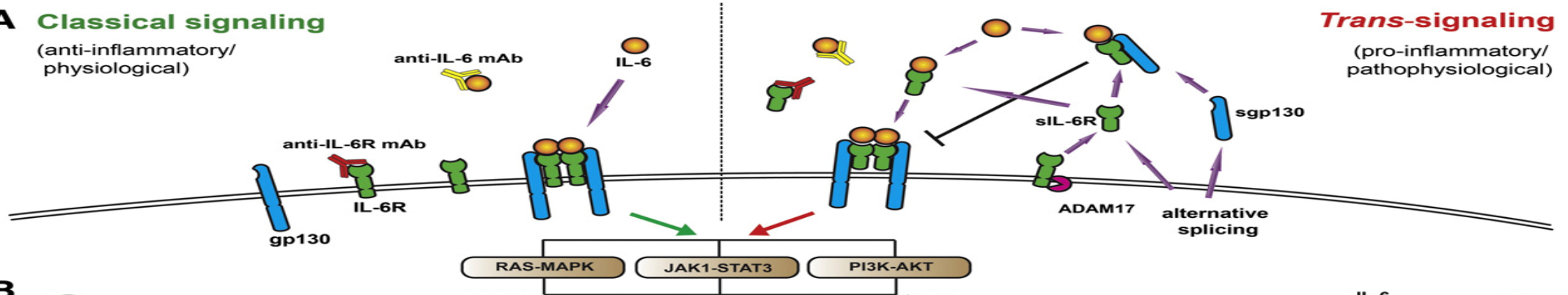
Examples



Typical Medical Model

A Classical signaling

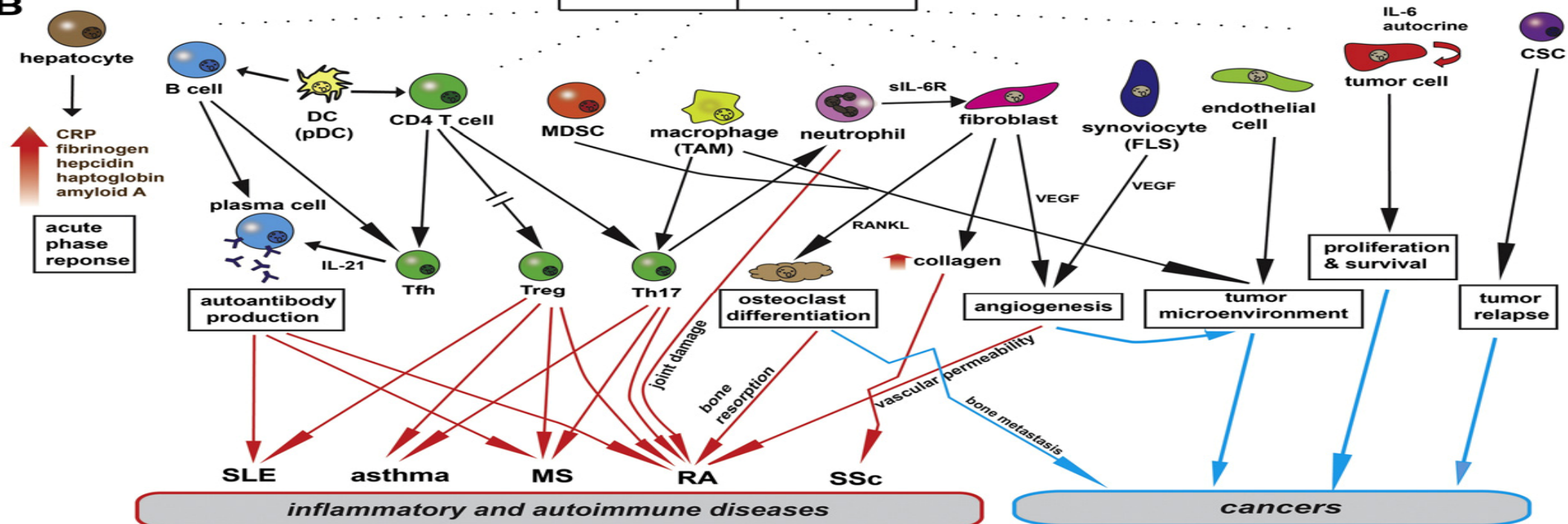
(anti-inflammatory/
physiological)



Trans-signaling

(pro-inflammatory/
pathophysiological)

B



Anti-inflammatory Drugs: Mechanisms

```
graph TD; A[Anti-inflammatory Drugs: Mechanisms] --> B[Decrease arachidonic acid metabolites]; A --> C[Decrease nitric oxide]; A --> D[Stabilize the vascular endothelium]; A --> E[Decrease TNF-α, IL-6, IL-1]; A --> F[Decrease complement activity]; A --> G[Inhibit histamine]; A --> H[Decrease leucocyte recruitment];
```

Decrease
arachidonic acid
metabolites

Decrease
nitric oxide

Stabilize the
vascular
endothelium

Decrease
TNF- α ,
IL-6, IL-1

Decrease
complement
activity

Decrease
leucocyte
recruitment

Inhibit
histamine

Drugs To Block TCs

Classification/Drug Target

Drugs

MABs

- | | |
|----------------------------|---|
| • Biological/TNF- α | adalimu, inflixu, certolizu, pegol, golimum |
| • Biological/IL-6 | tocilizu, siltuxi, sarilu |
| • Biological/IL-1 | rilonacept, canakinu |
| • Biological/IL-1 receptor | anakinra |

NIBs

- | | |
|---------------------------------|-------------------------|
| • Biological/Janus kinase 1,2,3 | ofacitinib, baricitinib |
|---------------------------------|-------------------------|

Medical Uses of Cytokines

Safety Cytokines

- Erythropoietin – anemia
- Granulocyte colony-stimulating factor – neutropenia
- Interleukin 11 - thrombocytopenia
- Bone Morphogenic Protein – orthopedics

Threat Cytokines

- Interferon alpha – hepatitis C
- Interferon beta – multiple sclerosis
- Interferon gamma – granulomatous disease
- Interleukin 2 – cancer

Functions of Threat Cytokines

- Inflammatory/Pain network — AA, PG, Sub P, CGRP, NMDA, etc
- Immune system — activation, swarming, destruction
- Endocrine system — hormone production and expression
- Metabolic system — catabolism, fuel source and metabolic rate
- Cardiovascular system — HR, HRv, syncope, shock
- Neurologic system — neurotransmitters, neurosignaling, ANS
- Psychologic system — anger, anxiety, depression, dissociation
- Sociologic system — selfish, reactive, impulsive, aggressive
- Spiritual system — isolated, disconnected, destructive
- Pain and suffering — amplification, sickness, hopeless, helpless

The Story

Threat-Defense Responses

One System – Bidirectional

Bottom Up - Physical – Connective tissues -> Brain

Top Down - Spiritual – Brain -> Connective tissues

SAME SOUP

Bottom Up
Tissue injury -> Fight then Flight

Connective tissues -> TCs -> Resource prioritization ->

Mobilization -> +Sugar for fuel (Catabolic) -> +Inflammation ->

+Immunity -> +SNS -> -PNS -> +Sensations -> +Limbic ->

-Cortex

Top Down
Trapped or losing -> Falter then Faint

Brain -> TCs -> Resource preservation -> Immobilization ->

--Cortex -> -Limbic -> -Sensory -> -PNS -> -SNS -> -Immunity ->

++Inflammation -> +Ketones for fuel (Catabolic)

Chronic

Threat ←-----→ Safety

TCs

- Ill
- Inflamed
- Degenerative
- Isolated
- Pain
- Suffering

SCs

- Well
- Chilled
- Regenerative
- Connected
- Harmony
- Thriving

Monoclonal Antibodies
?????

Safety

?????

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