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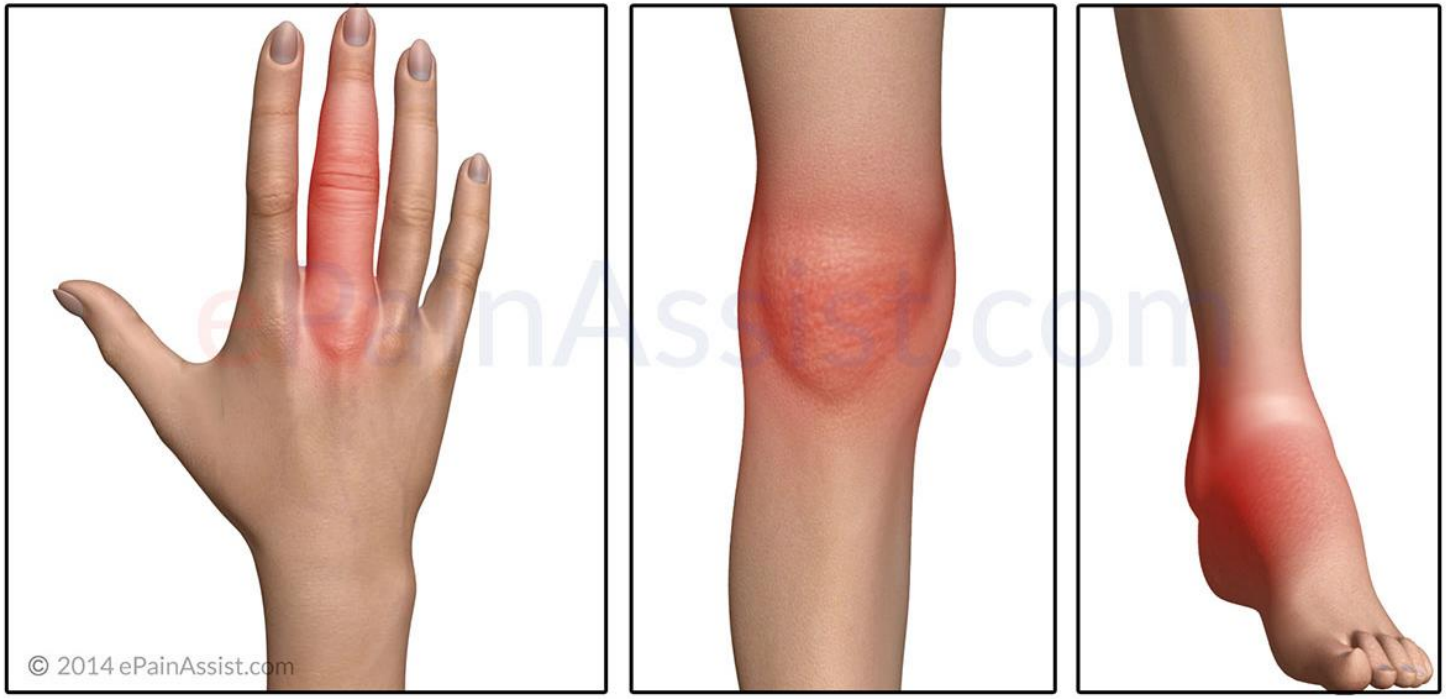
Mathematical Modeling of Immunopathogenesis of Rheumatoid Arthritis

K. Odisharia, V. Odisharia, P. Tsereteli, N. Janikashvili

St. Andrew the First-Called Georgian University of the Patriarchate of Georgia
Iv. Javakhishvili Tbilisi State University
Tbilisi Sate Medical University
Georgian Association of BioMathematics

Rheumatoid Arthritis

- **Rheumatoid arthritis (RA) is a long-lasting immune mediated disorder**
- **RA may affect different joints**
- **Clinical signs of RA include redness, swelling and pain around the joint area**



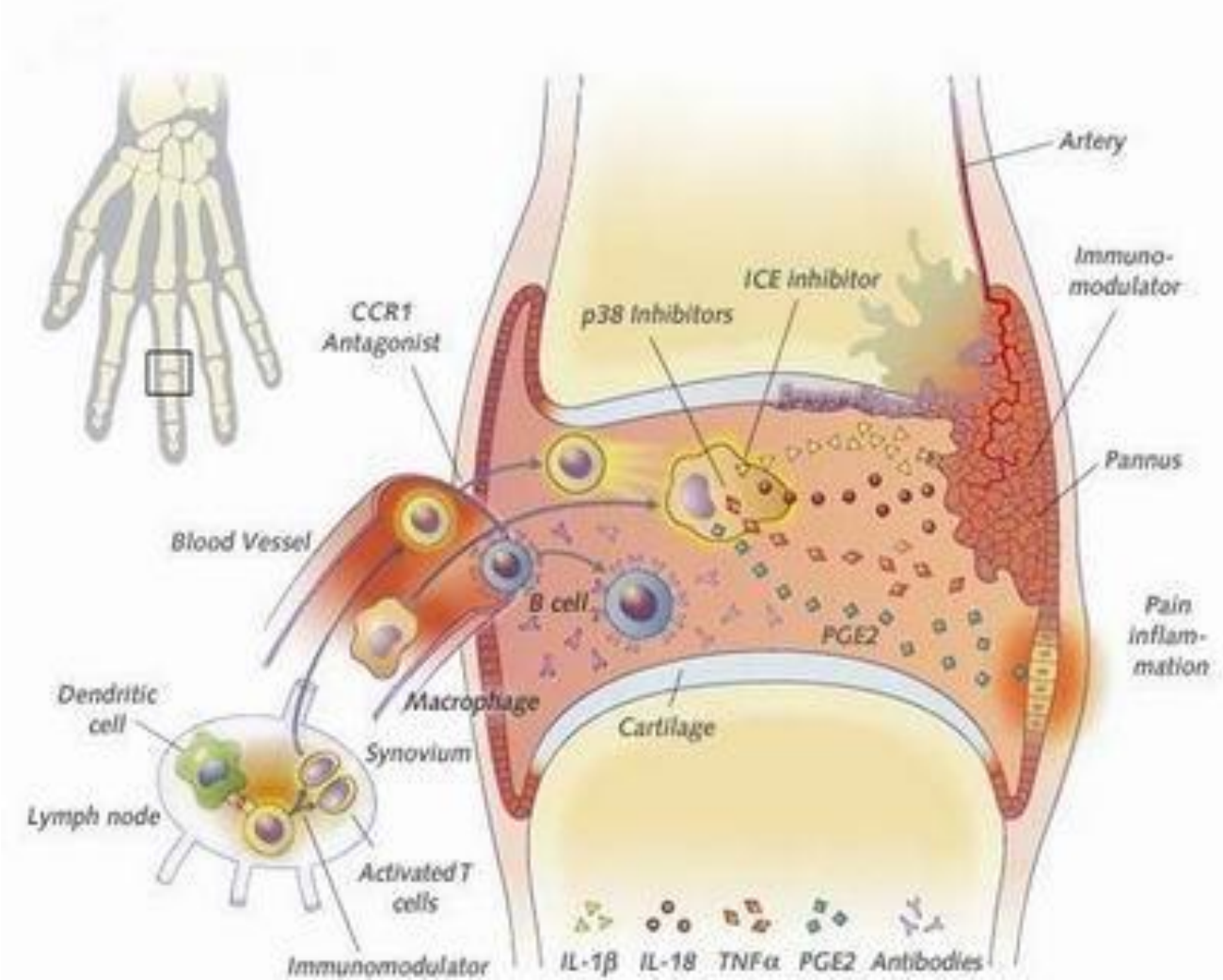
Rheumatoid Arthritis

- **RA is an autoimmune disorder that involves the cartilage destruction, bone damage and the joint inflammation**

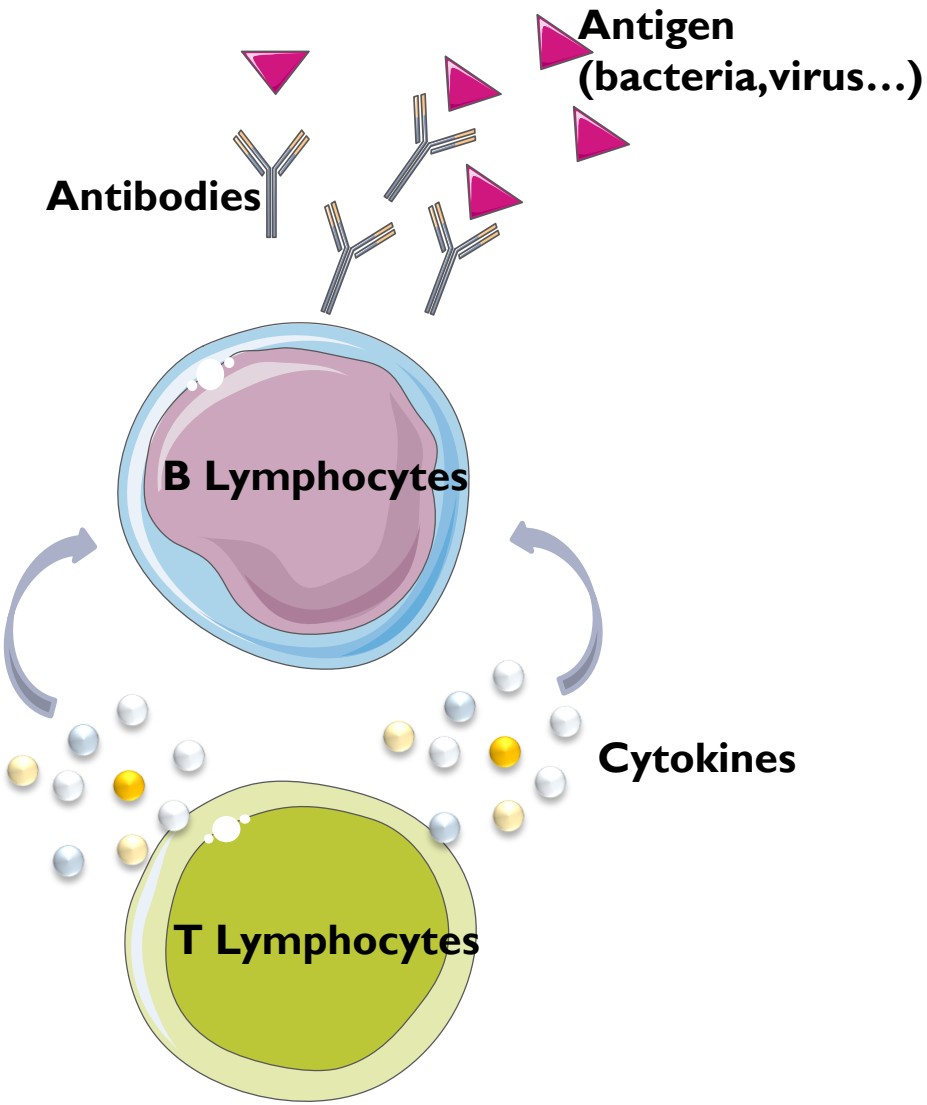
Immunopathogenesis of Rheumatoid Arthritis

- **Complex process that involves:**

  B lymphocytes and T lymphocytes

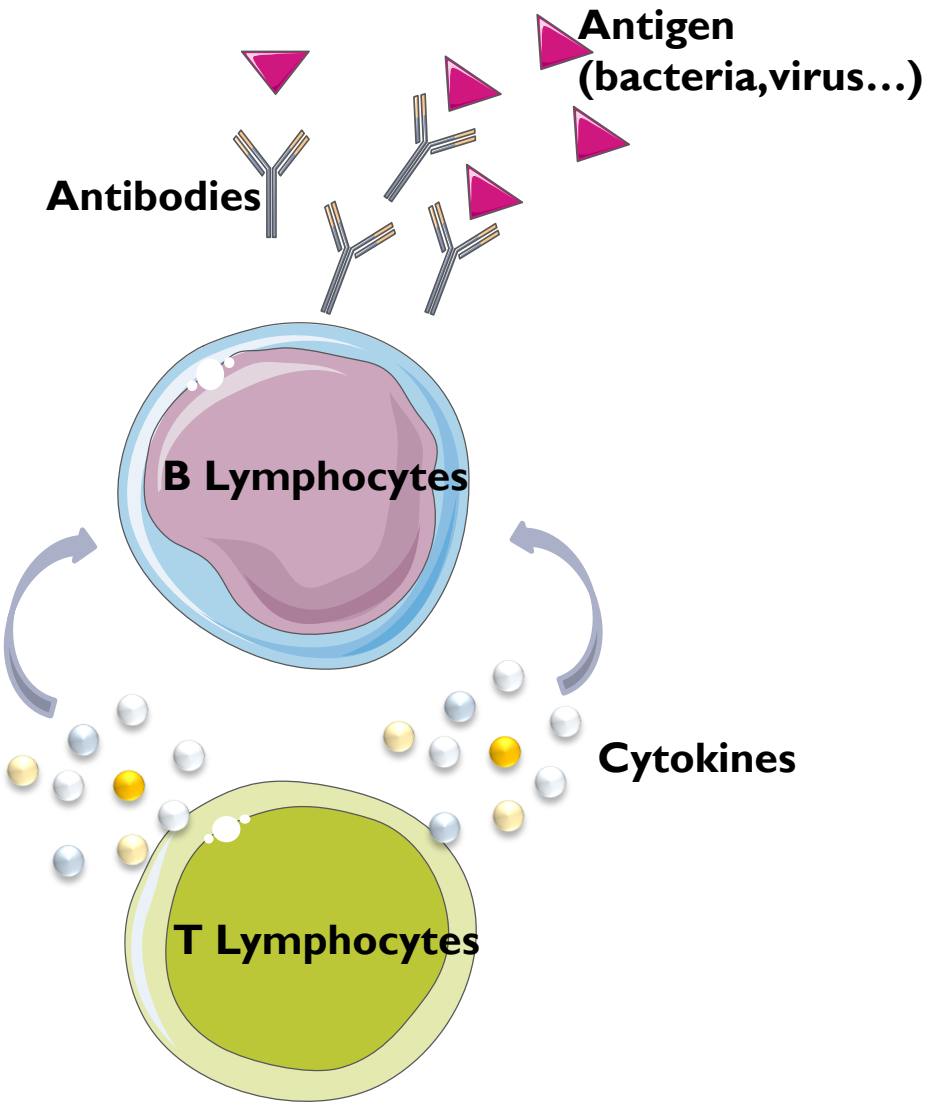


Immune response



Immune response

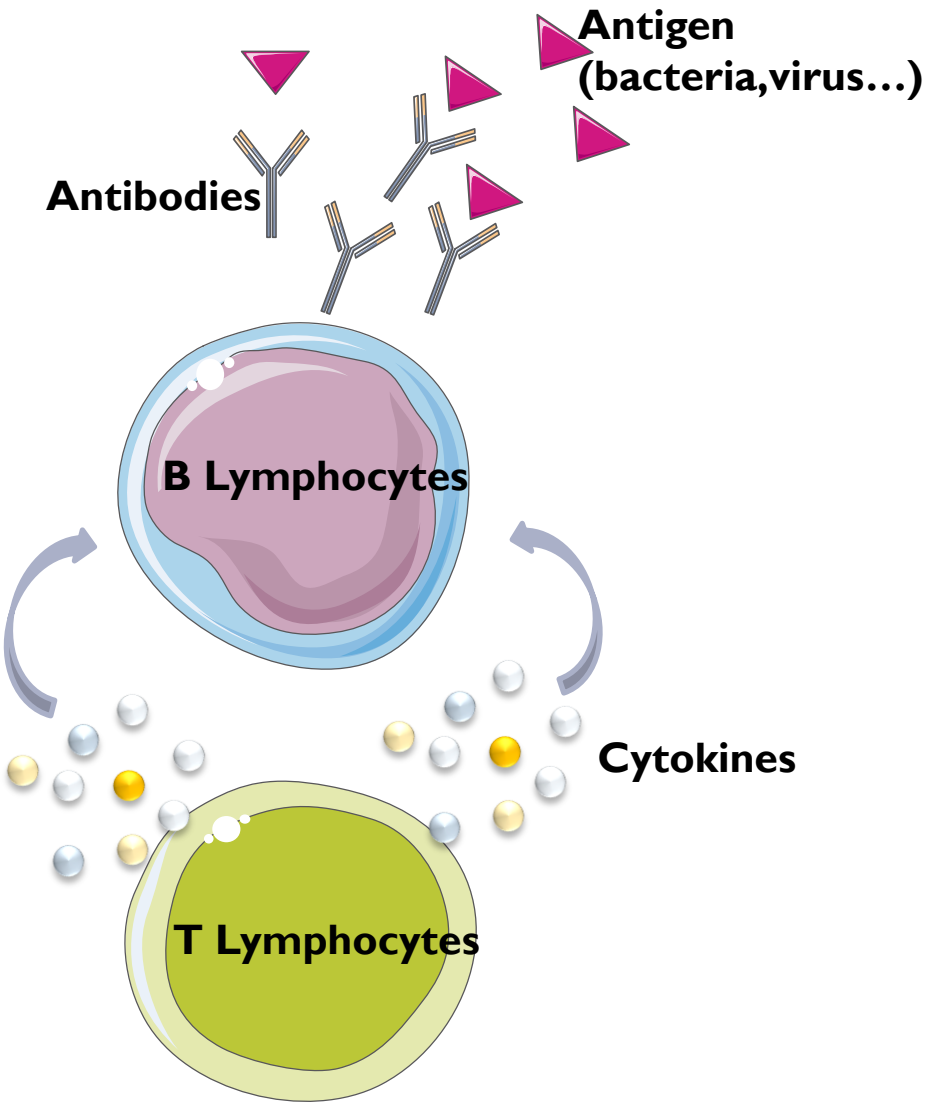
<u>B lymphocytes</u> ***are a subset of white blood cells, which secrete antibodies.***
Antibodies specifically bind to the foreign antigen, allowing its removal.



Immune response

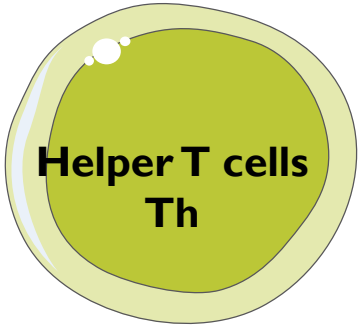
B lymphocytes *are a subset of white blood cells, which secrete antibodies.*
Antibodies specifically bind to the foreign antigen, allowing its removal.

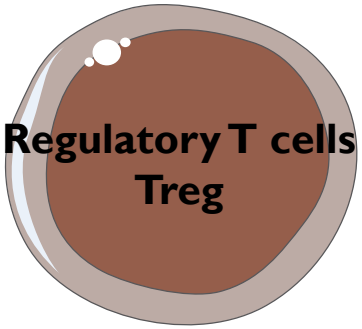
T lymphocytes *are a subset of white blood cells, which secrete cytokines.*
Type and nature of cytokines guide the immune response by activating or suppressing other immune cells including B lymphocytes.



T lymphocytes

- **There are several different types of T lymphocytes, among them are:**





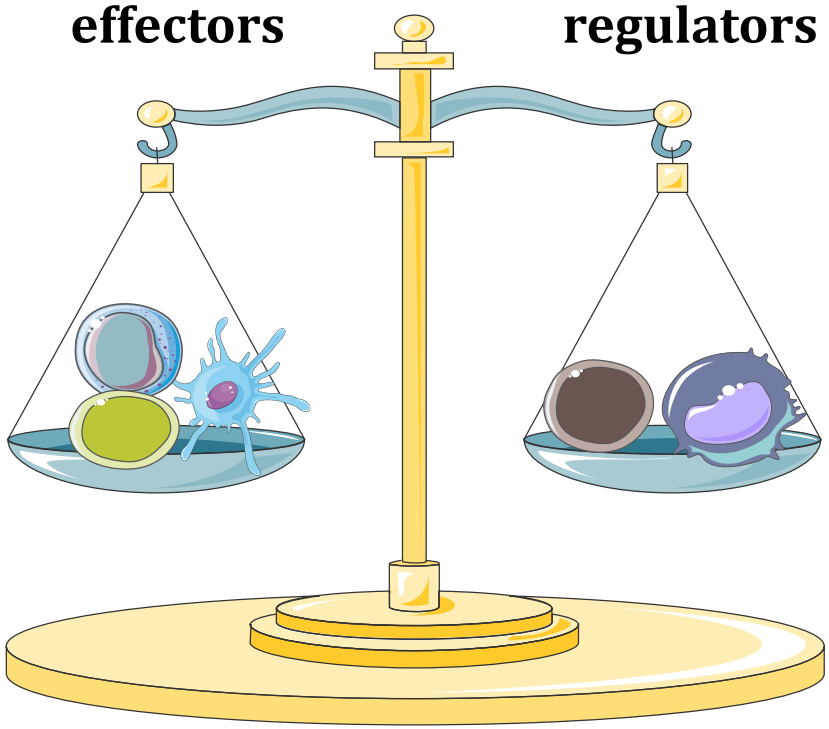
Provide help to other cells in the immune response by activating T and B cells.

Th play a critical role in immune activation and prevention of immunodeficiency and cancer

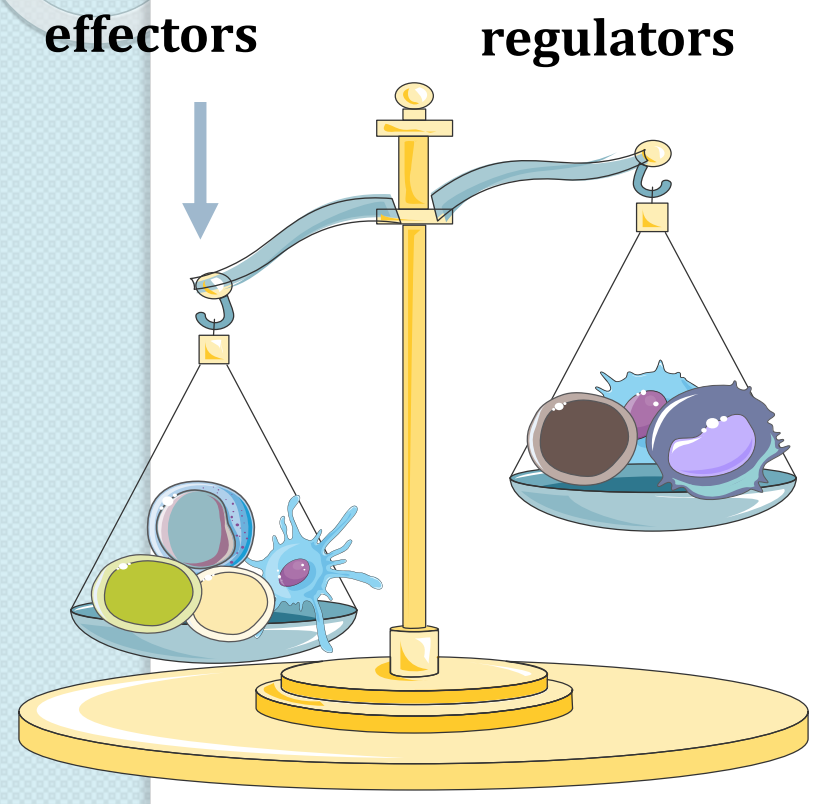
Regulate the other immune cells by suppressing their activity.

Treg play a critical role in the prevention of inflammation and autoimmunity

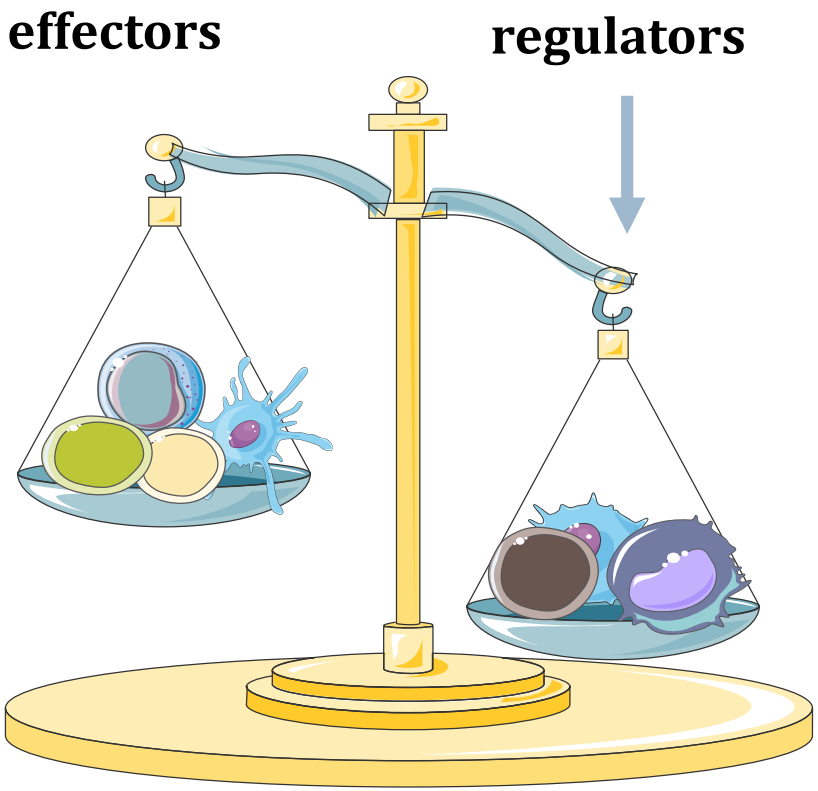
Immune balance



Immune balance

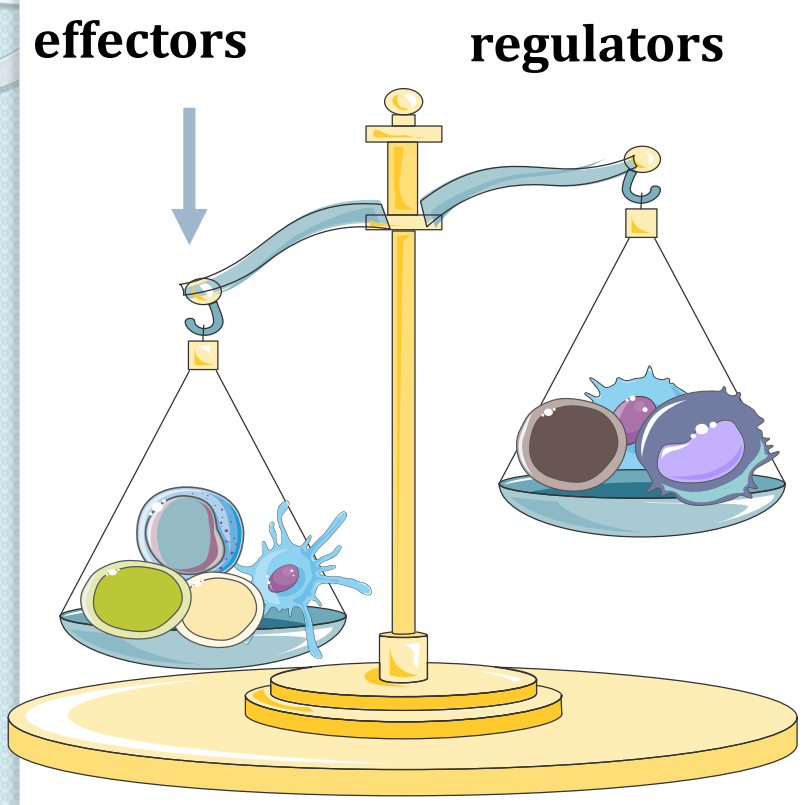


Inflammation



Immunodeficiencies

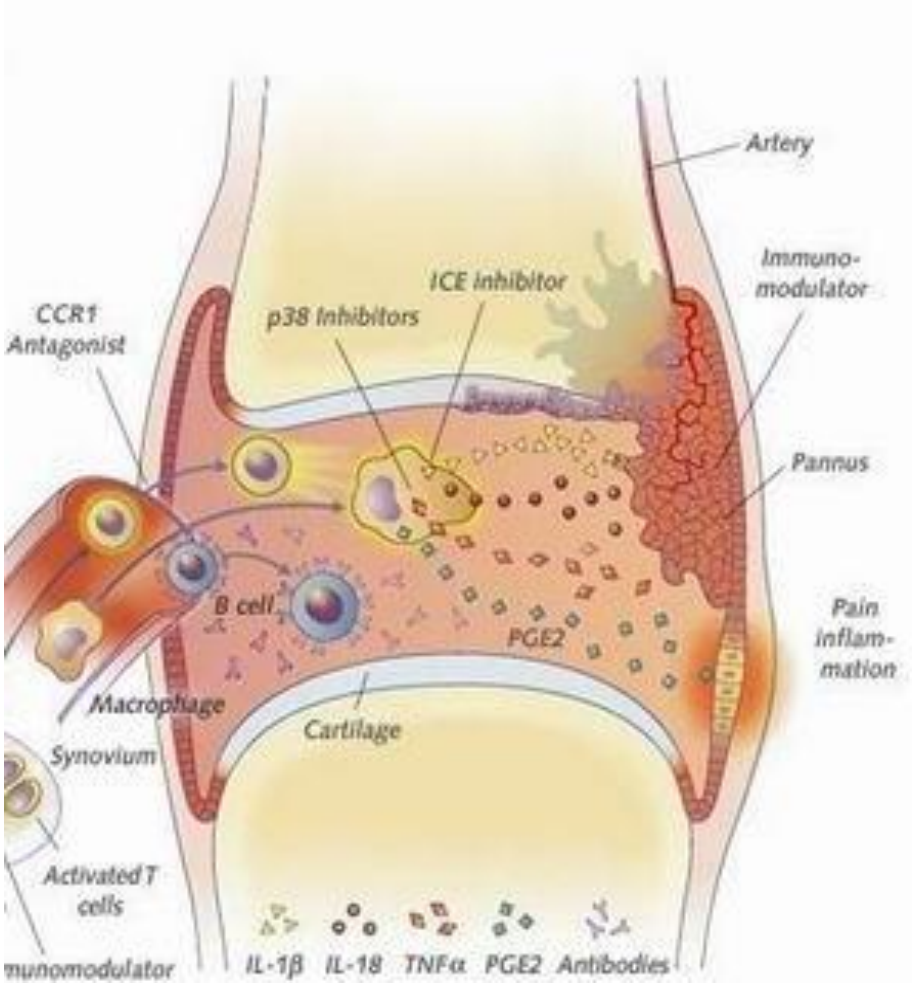
Autoimmunity



Autoimmunity occurs when the immune system fails to properly distinguish between "self" and "non-self",
and attacks part of the body inducing strong inflammatory response against self substances

Inflammation

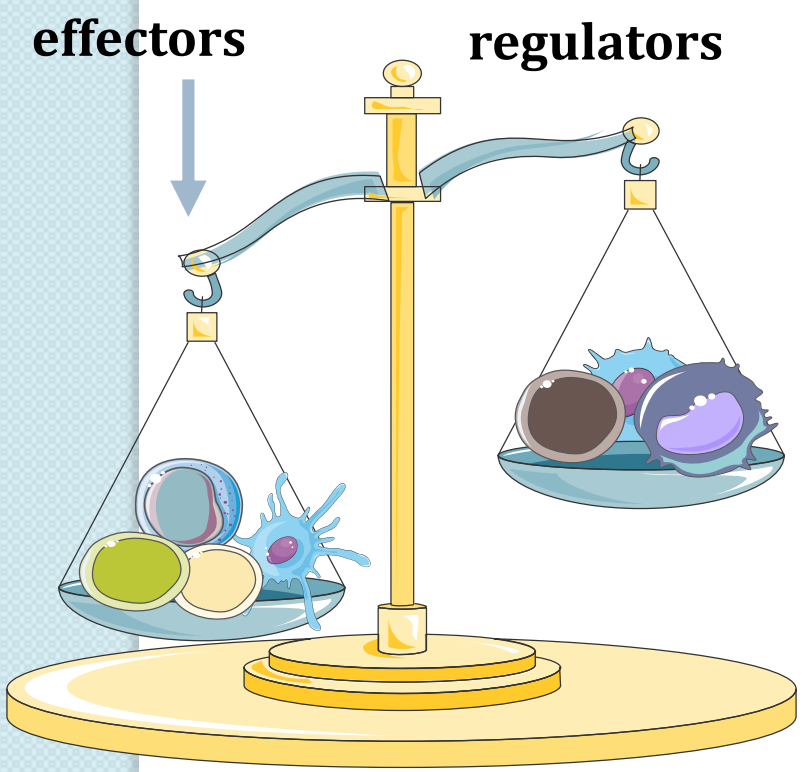
Immunopathogenesis of Rheumatoid Arthritis



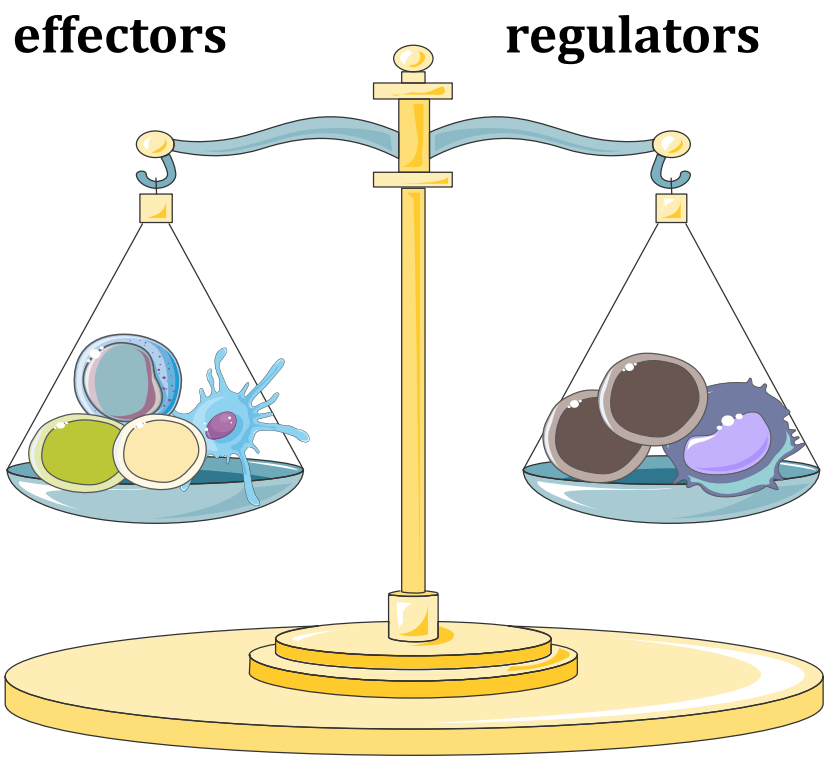
- **Autoreactive B cells** that produce antibodies against the cartilage of the joint and destroy it
- **Helper T cells** that stimulate the growth of autoreactive B cell clone
- **Regulatory T cells** that are diminished and unable to regulate the growth of helper T cell and autoreactive B cell

Treatment of Rheumatoid Arthritis

- **Immunotherapy of Rheumatoid Arthritis aims to restore the dysregulated immune balance**



Inflammation



Cure

Treatment of Rheumatoid Arthritis

Tocilizumab

(Anti-interleukine-6-receptor antibodies)

A novel immunotherapeutic drug

Recent preclinical and clinical trials show that Tocilizumab specifically blocks Helper T cell growth and transforms them to regulatory T cells, e.i. restores Th / Treg balance

Therefore, this drug is the most prospective therapy in Rheumatoid Arthritis

Current medical problem is the optimization of treatment dose and duration for each individual patient

Mathematical Modeling of Immunopathogenesis of Rheumatoid Arthritis

- **The first objective:**

  To establish a mathematical model that describes the immunopathogenesis of RA using non-linear differential equations

- **The second objective:**

  Using our mathematical model, to provide a mechanistic interpretation of immunotherapeutic effects of Tocilizumab which deals with the dose efficacy of the treatment

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Assumptions

- Autoreactive B cells grow logistically in response to the self-antigens of the cartilage
- Helper T cells grow logistically
- Helper T cells stimulate the growth of autoreactive B cells => disease progresses
- Source of regulatory T cells is considered outside of the system
- Regulatory T cells suppress the growth of B cells and helper T cells => disease regresses

Designations

J(t) – Joint (cartilage) amount at time t

B(t) – number of autoreactive B cells at time t

$T_h(t)$ – number of Helper T cells at time t

$T_{reg}(t)$ – number of regulatory T cells at time t

Logistic growth

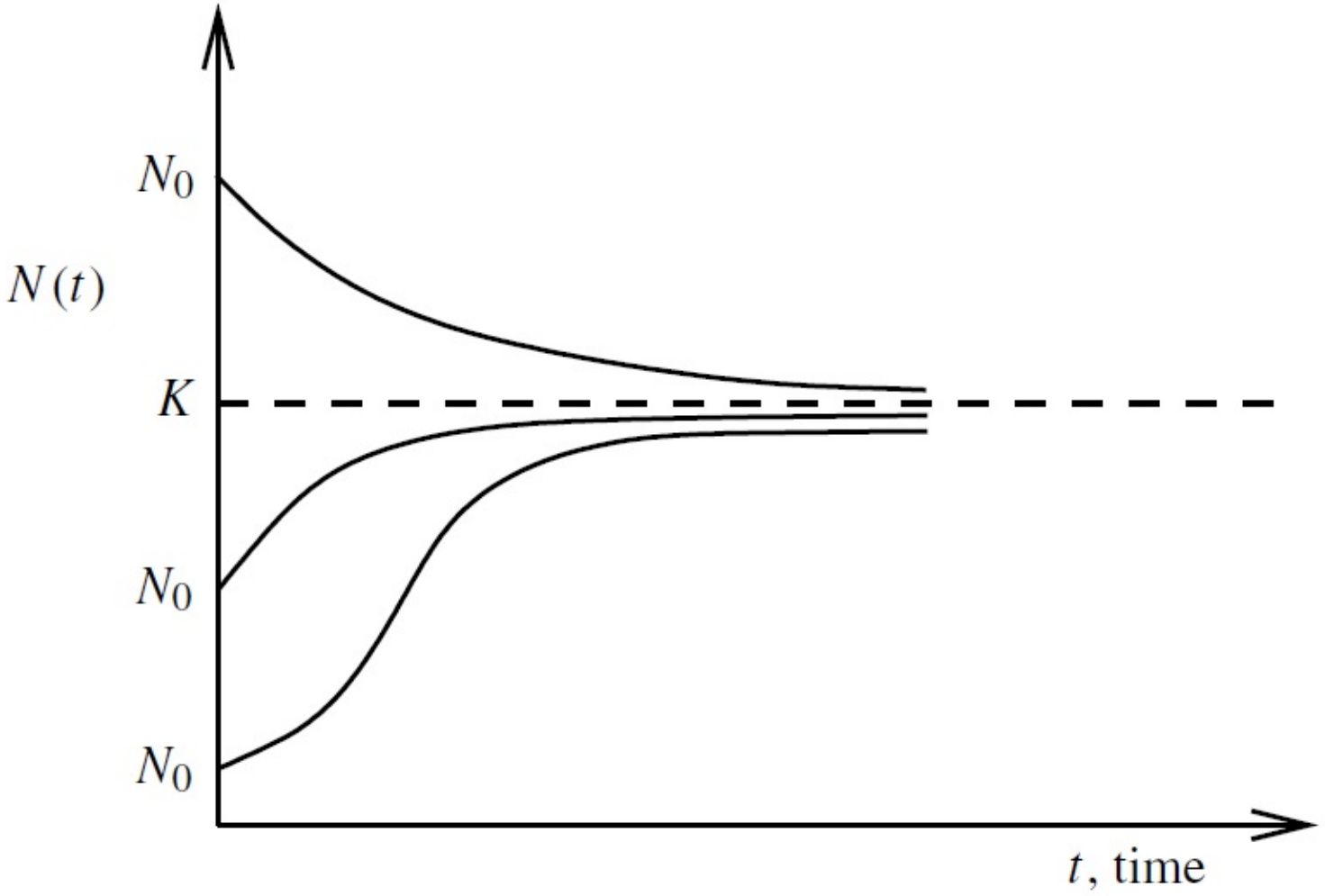
$$\frac{dN}{dt} = rN\left(1 - N/K\right)$$

r and K *are positive numbers*

If $N(0) = N_0$

$$N(t) = \frac{N_0 K e^{rt}}{\left[K + N_0\left(e^{rt} - 1\right)\right]} \to K$$

Logistic growth



B cells equation

$r_1 B(t)\left(1 - b_1 B(t)\right)$ *Logistically growth*

$c_1 B(t) T_h(t)$ *Stimulated growth*

$d_1 B(t) T_{reg}(t)$ *Suppression*

$$\frac{dB}{dt} = r_1 B(t)\left(1 - b_1 B(t)\right) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t)$$

Helper T cells equation

$r_2 T_h(t)\left(1 - b_2 T_h(t)\right)$ *Logistically growth*

$$\frac{dT_h}{dt} = r_2 T_h(t)\left(1 - b_2 T_h(t)\right)$$

Regulatory T cells equation

$s_2 - d_2 T_{reg}(t)$ *Growth*

$$\frac{dT_{reg}}{dt} = s_2 - d_2 T_{reg}$$

Joint (cartilage) equation

$$\frac{dJ(t)}{dt} = -a_1 J(t)\left(B(t) - B^{norm}\right)$$

$$a_1 > 0$$

$$B(t) \geq B^{norm}$$

Mathematical model

$$\frac{dJ(t)}{dt} = -a_1 J(t)\left(B(t) - B^{norm}\right)$$

$$\frac{dB}{dt} = r_1 B(t)\left(1 - b_1 B(t)\right) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t)$$

$$\frac{dT_h}{dt} = r_2 T_h(t)\left(1 - b_2 T_h(t)\right)$$

$$\frac{dT_{reg}}{dt} = s_2 - d_2 T_{reg}$$

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Drug effects: assumptions

- The drug blocks helper T cells growth
- The drug transforms part of helper T cells into regulatory T cells

Drug effects: equation

$$F(u) = a\left(1 - e^{-mu}\right)$$

$$a > 0 \quad m > 0$$

$F(u)$ **Is fractional cell transformation or suppression for a given amount of drug *u*, at the arthritis side**

$$\frac{du(t)}{dt} = v(t) - d_3 u(t)$$

$v(t)$ **Drug dose**

d_3 **Per capita decay rate of the drug once it is injected. It incorporates all pathways of elimination of the drug**

Mathematical model with the drug

$$\frac{dJ(t)}{dt} = -a_1 J(t)\left(B(t) - B^{norm}\right)$$

$$\frac{dB}{dt} = r_1 B(t)\left(1 - b_1 B(t)\right) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t)$$

$$\frac{dT_h}{dt} = r_2 T_h(t)\left(1 - b_2 T_h(t)\right) - k_1\left(1 - e^{-m_1 u}\right) T_h - k_2\left(1 - e^{-m_2 u}\right) T_h$$

$$\frac{dT_{reg}}{dt} = s_2 - d_2 T_{reg} + k_2\left(1 - e^{-m_2 u}\right) T_h$$

$$\frac{du(t)}{dt} = v(t) - d_3 u(t)$$

Conclusions

This is a novel mathematical model that explores the functional dynamics of cartilage destruction during RA.

The model explains:

- ✓ **Interactions between autoreactive B lymphocytes and T cell subsets**
- ✓ **Helper T lymphocyte and regulatory T lymphocyte interactions**
- ✓ **Fractional cell transformation from helper T cells to regulatory T cells for a given amount of drug**
- ✓ **Optimization of the injection frequencies**

Acknowledgement

Team & Collaborators

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