



Emerging Technologies For Immune Tolerization

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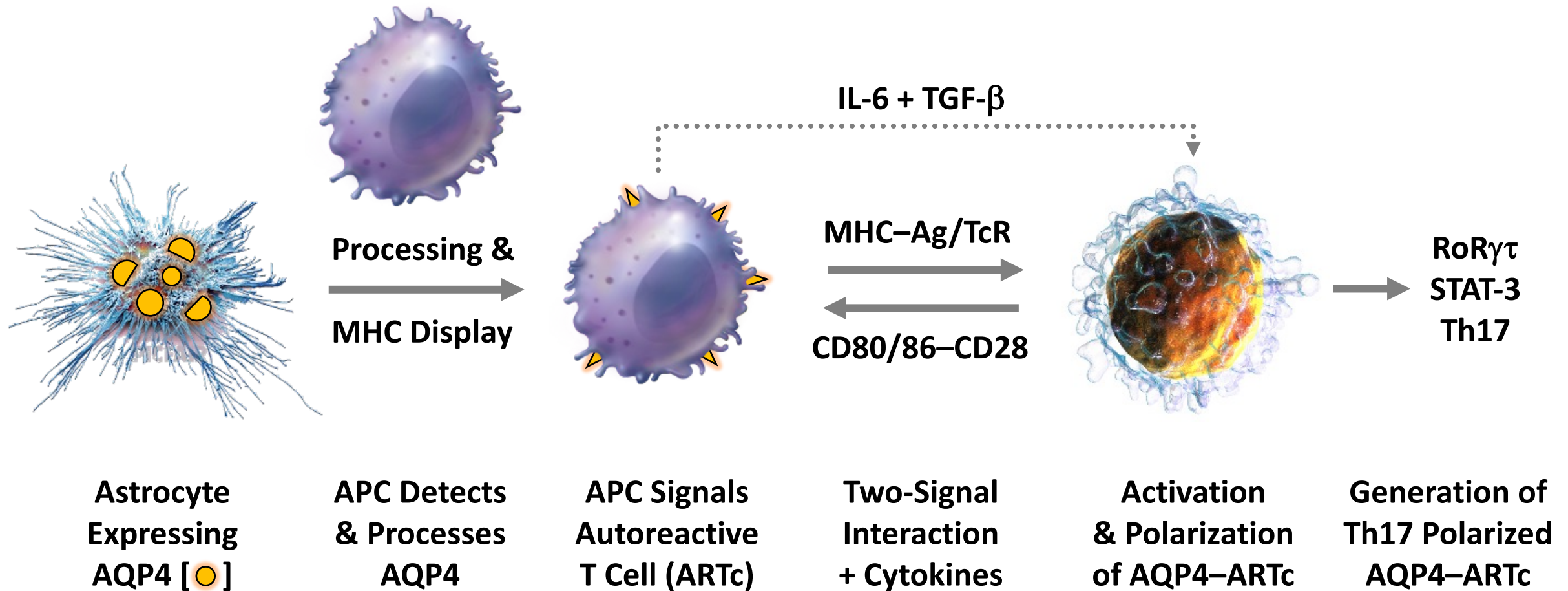
Disclosures

- **Founder:** NovaDigm Therapeutics, Inc. (vaccines)
Tegos Therapeutics, LLC (anti-infectives)
ImmunoTx, LLC (immunotherapeutics)
Metacin, Inc. (music neuroscience)
- **Grants:**

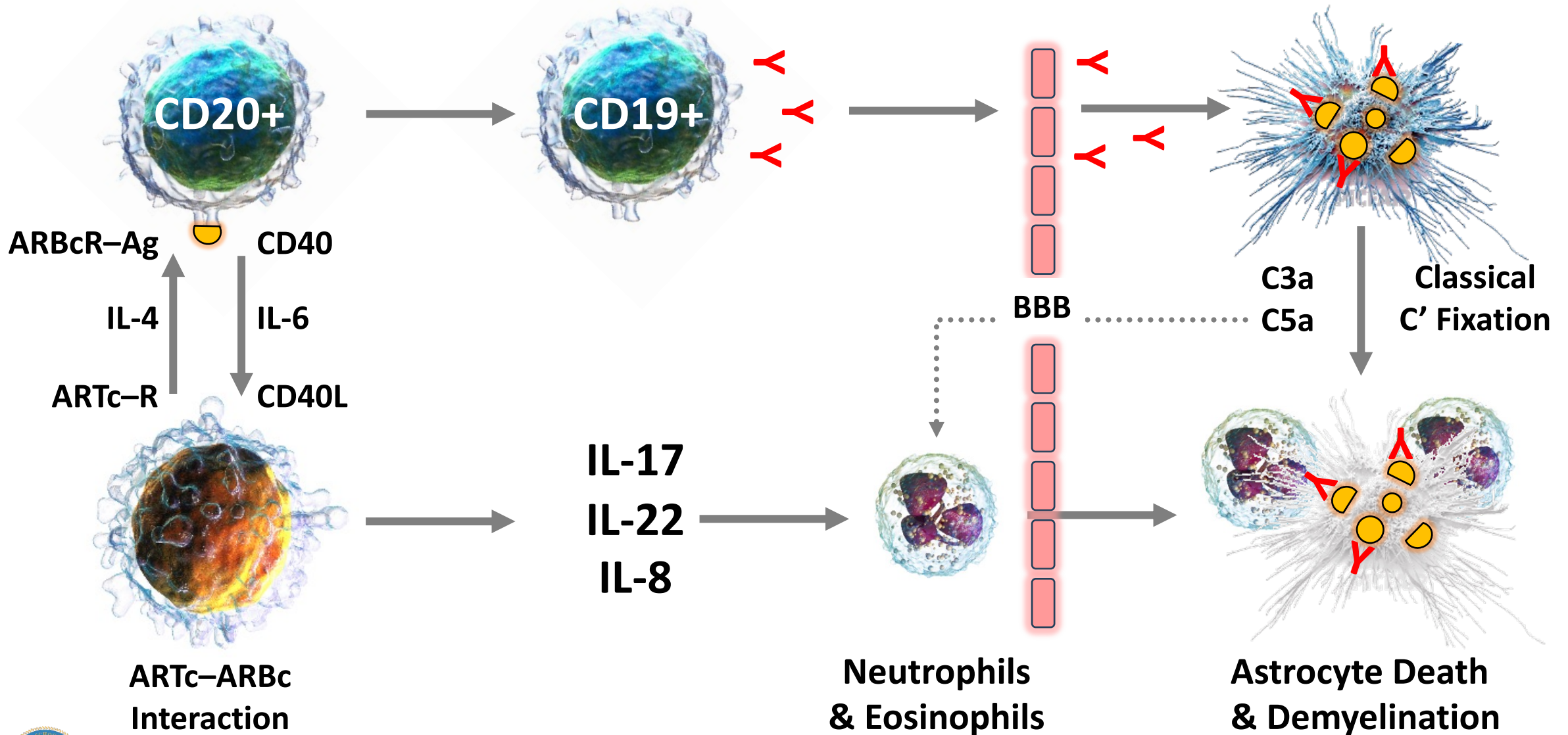
NIH U19 AI-172713	NIH R01 AI-139244
NIH U01 AI-124319	NIH COVID-19 SPARTA
NIH R01 AI-309241	DoD CDMRP JW-190421
NIH R01 AI-310380	DoD CDMRP JW-160125
- **Advisor:** Advisor, Guthy-Jackson Charitable Foundation
AstraZeneca; Genentech–Roche; Amgen
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Pathogenesis

Current Understanding: Pathophysiology in NMO



Current Understanding: Pathophysiology in NMO



Immune Tolerance

What is Immune Tolerance ?

Immune tolerance is how your immune system protects you against internal or external threats such as cancer or infection, without harming any healthy molecules, cells or tissues that make up the body.

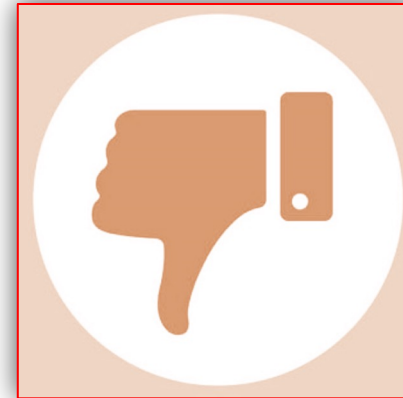
Put another way, immune tolerance is the system of checks & balances that prevents the immune system from targeting healthy cells and tissues.

Immune System Discerns Self vs. Non-Self

Healthy Molecules
Healthy Cells
Healthy Tissues
Wound Healing
Normal Growth

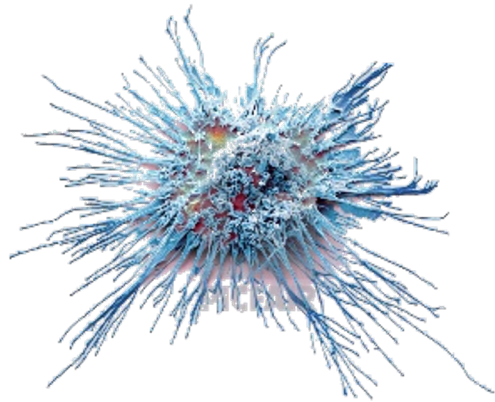


Immune
System

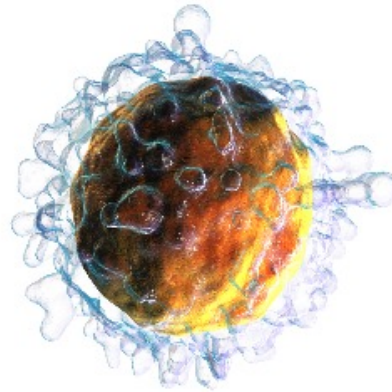


Pathogenic Microbes
Pre-Cancerous Cells
Cancers or Tumors
Poor Wound Healing
Abnormal Growth

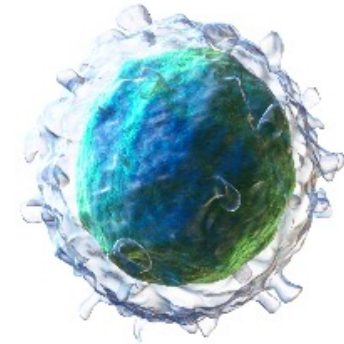
Which Cells are Key to Tolerization ?



**Antigen
Presenting Cells**

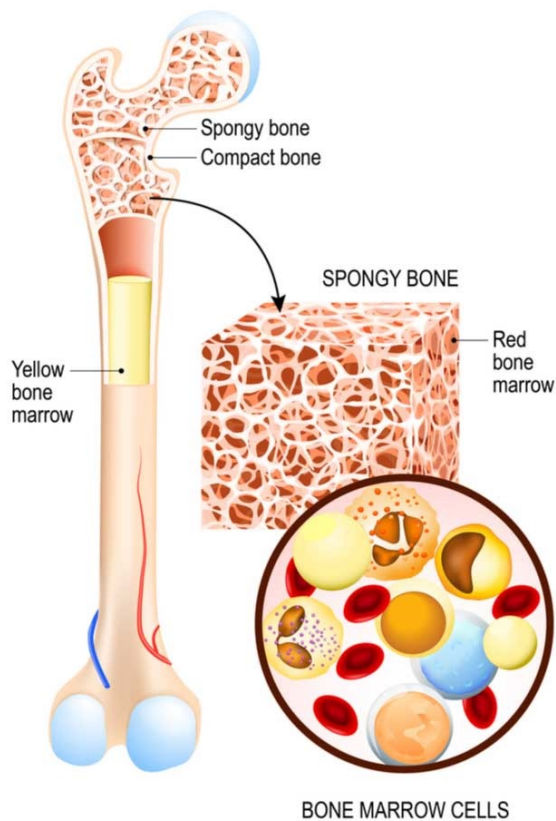


**T Cells
(T Lymphocytes)**

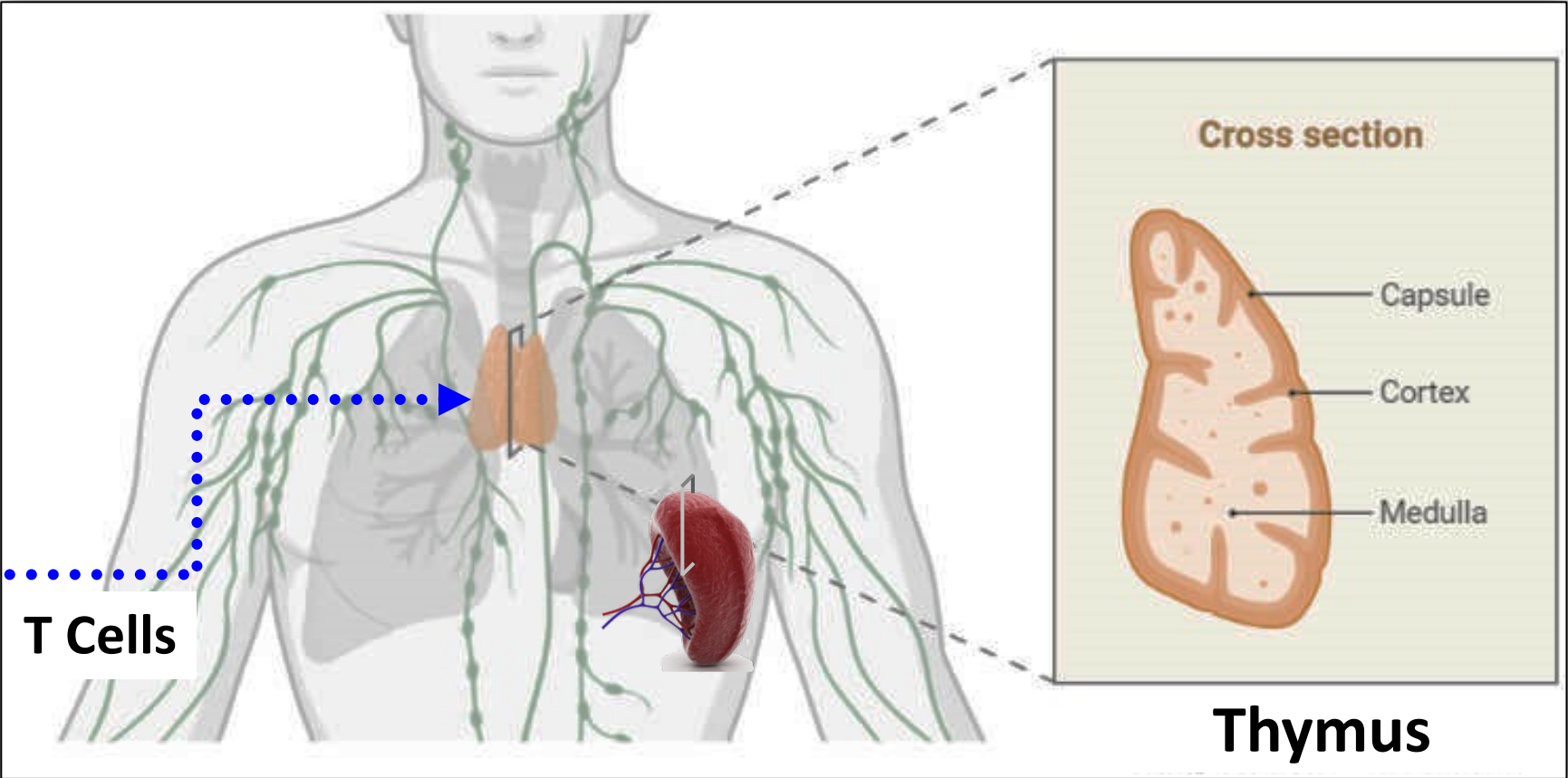


**B Cells
(B Lymphocytes)**

The Thymus: T Cell University

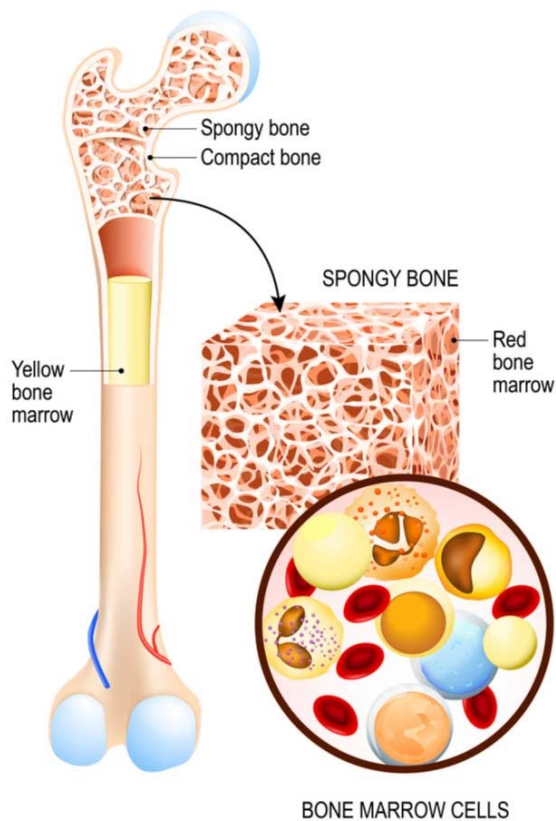


T cells
B cells
White Blood Cells
Red Blood Cells

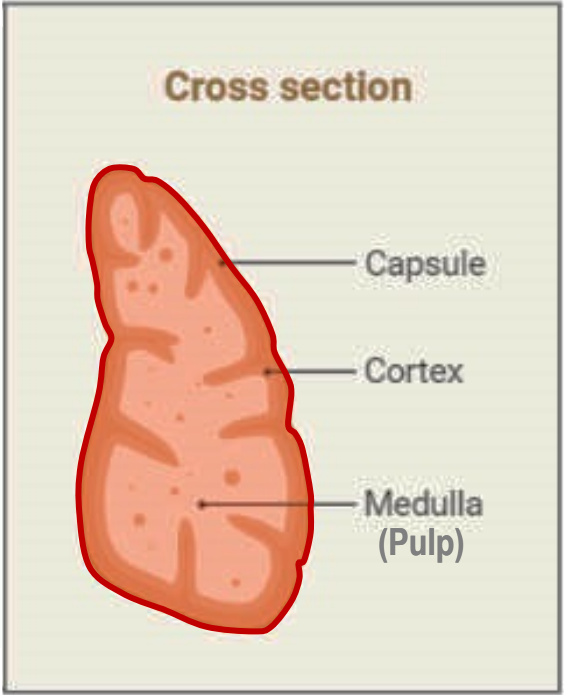


T cells made in the bone marrow move to the **thymus** to be tested three ways

The Spleen: B Cell University



B Cells



Spleen

T cells

B cells

White Blood Cells

Red Blood Cells

B cells made in the bone marrow move to the spleen to be tested three ways

T Cells & B Cells Must Pass Three Exams:

1. Can they recognize the antigen-presenting cell ?

Yes 

No  Removal [-]

2. Can they do the molecular handshake with APC ?

Yes  [+]

No  Removal

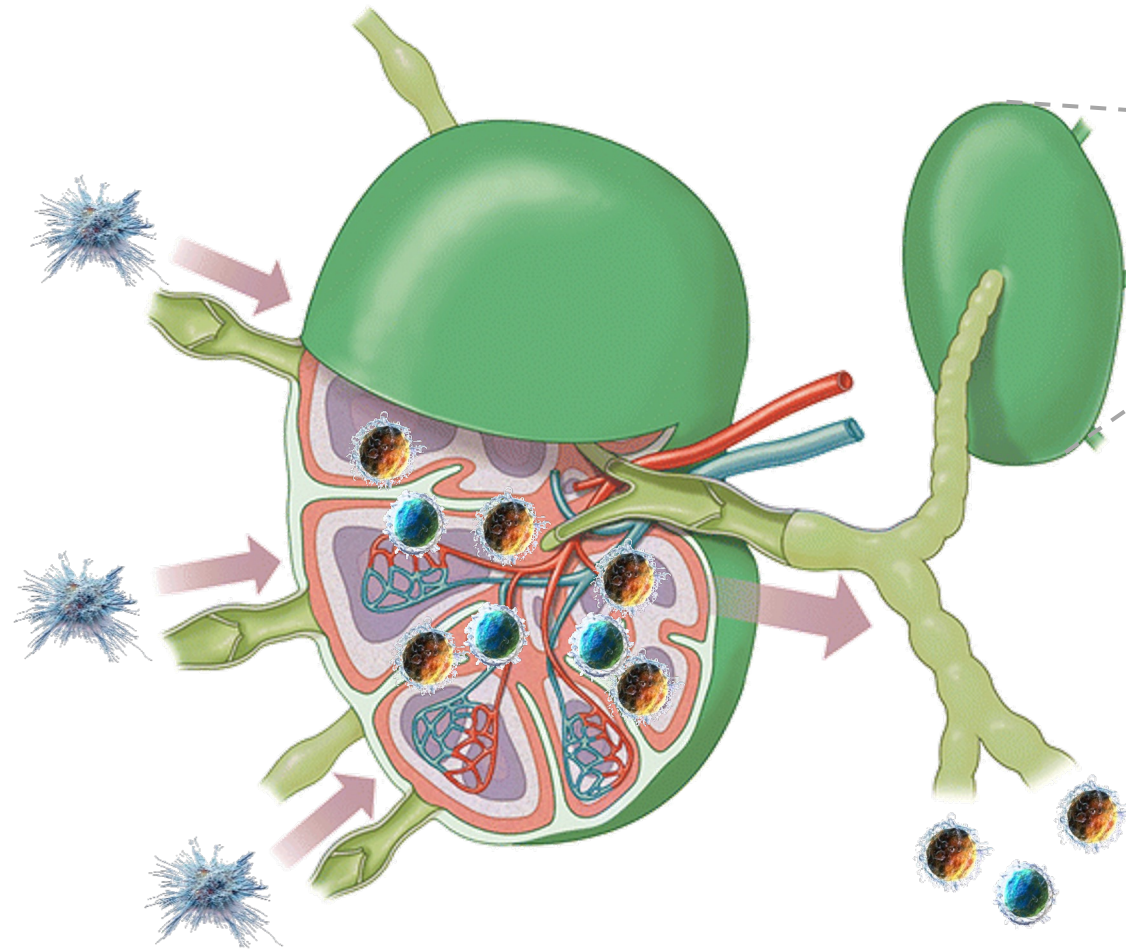
3. Can they distinguish between self vs. non-self ?

Yes 

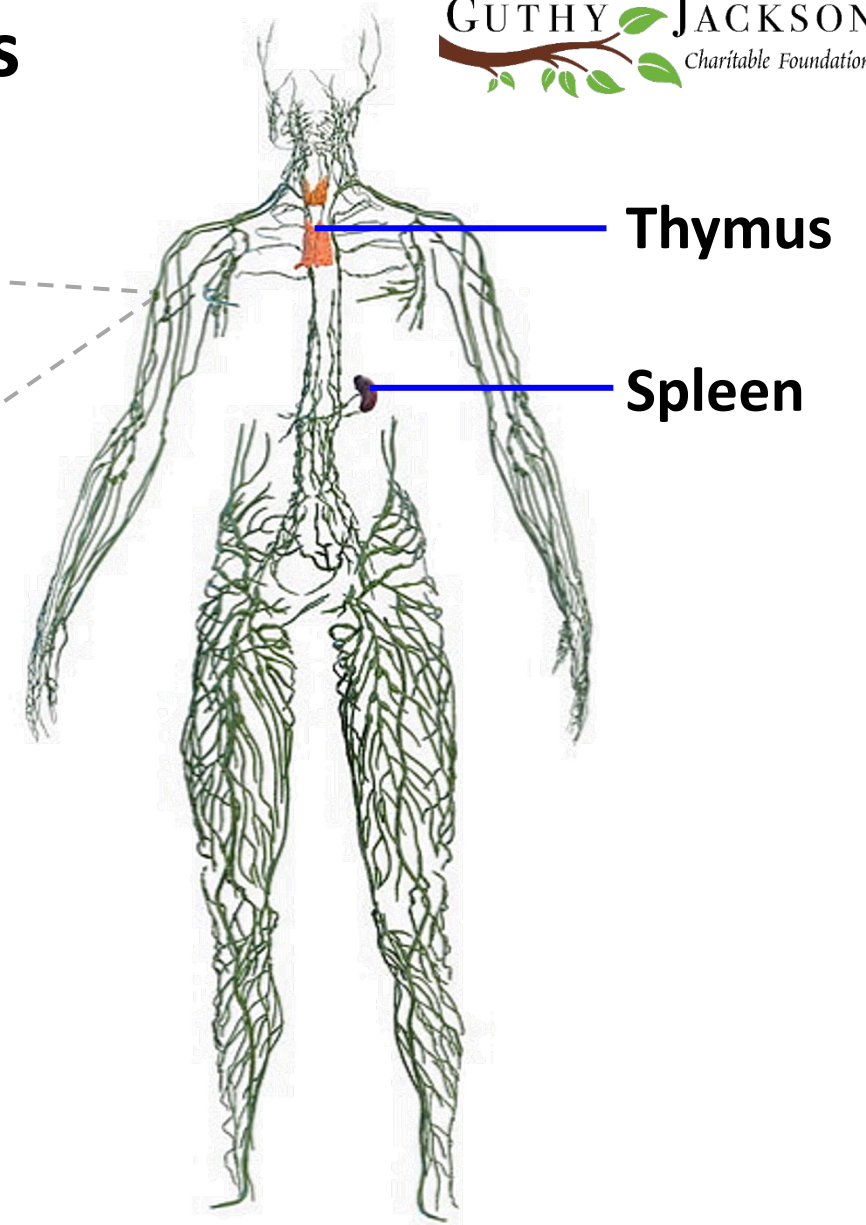
No  Removal [-]

Only 1% of T and B cells Successfully Pass All Three Exams

Graduate T & B Cells Move to Lymphatics



Lymph Node

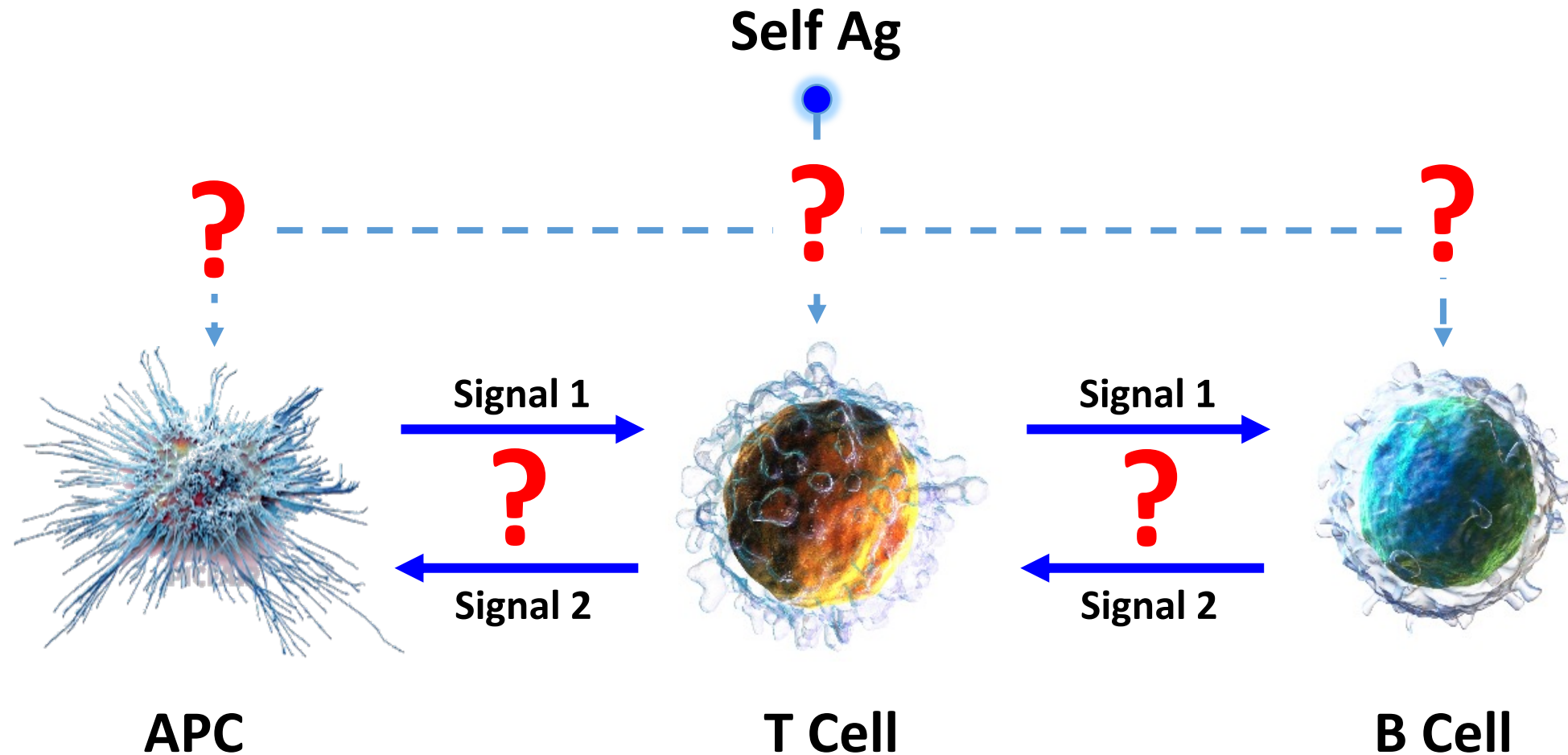


Thymus

Spleen

**How is
Immune Tolerance Lost ?**

Loss of Immune Tolerance: Mistaken Identity



What Causes Loss of Immune Tolerance ?



Abnormal Place or Structure of Self-Ag

DNA / RNA



Dysfunctional Antigen Presenting Genes

MHC System



Dysfunctional T or B Cell Receptor Genes

RAG System



Infectious Disease, Neoplasia or Cancer

Ag Mimicry

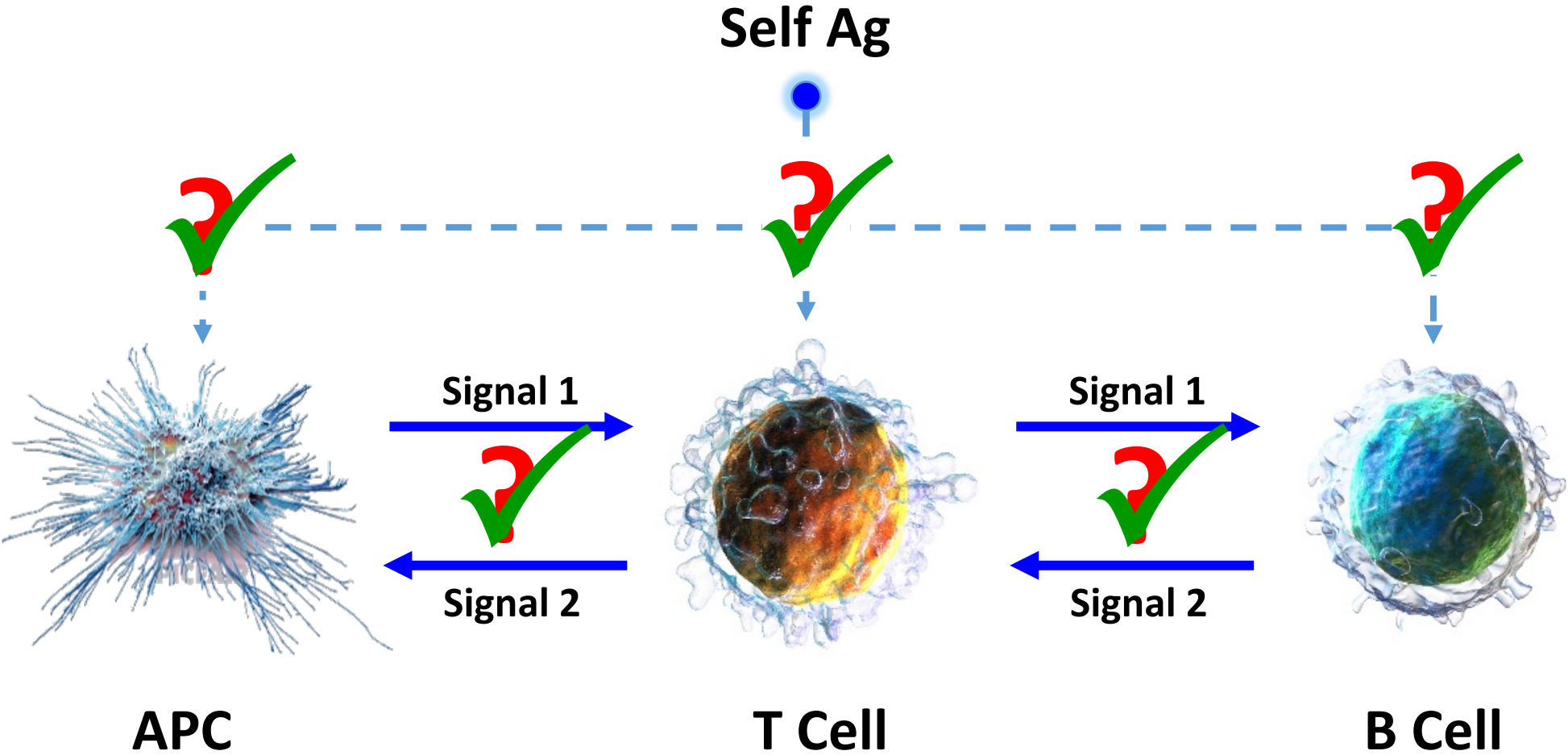


Pregnancy or Allograft Transplantation

HLA System

**How Can
Immune Tolerance be Restored ?**

Restoring Immune Tolerance



How Immune Tolerance be Restored ?



Correct Gene Mutations or Dysfunction

DNA Editing



Correct Production or Protein Structure

RNA / Folding



Reprioritize APC, T cell, B cell Response

Deviation



Delete Auto-Reactive APCs, T or B cells

Censoring

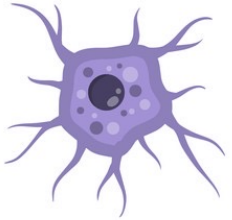


Re-Educate APCs, T cells and/or B cells

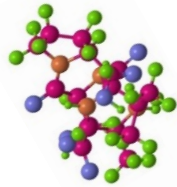
Re-Program

Technologies

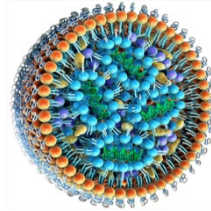
Emerging Technologies Focus on NMO Tolerization



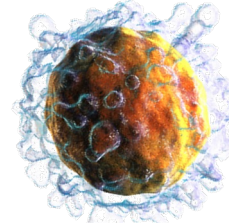
**Dendritic Cell
Vaccines**



**Engineered
Epitopes**



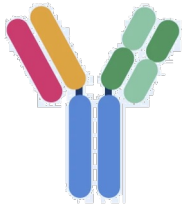
**Tolerizing
NPs**



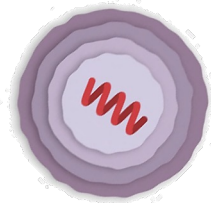
**CA/ART
Therapy**



**Ag-Specific
CP Inhibition**



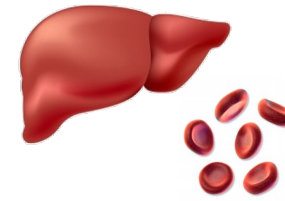
**HLA-G
Tolerance**



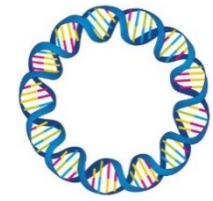
**Inverse
Vaccines**



**Marrow
Rebooting**

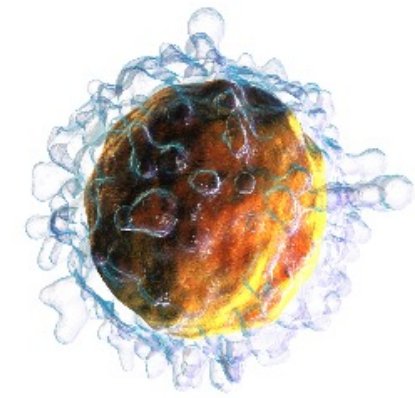


**Endogenous
Tolerance**



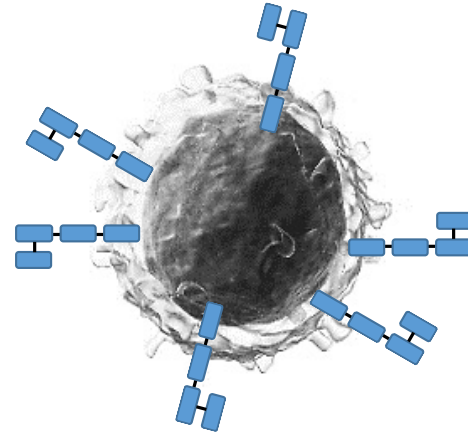
**Programmed
Cell Death**

Example: CAR-T or CAAR-T Cell Therapy



**Healthy T Cell
(from Patient)**

CA/AR 
Modify in Lab



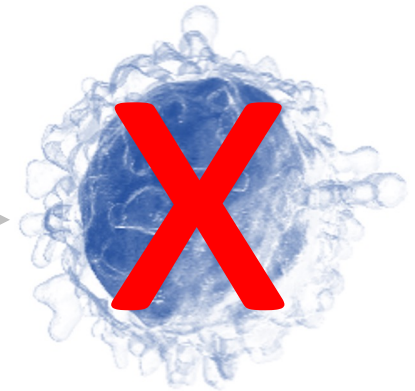
**CAR-T or CAAR-T Cell
(Return to Patient)**

Delete

Delete

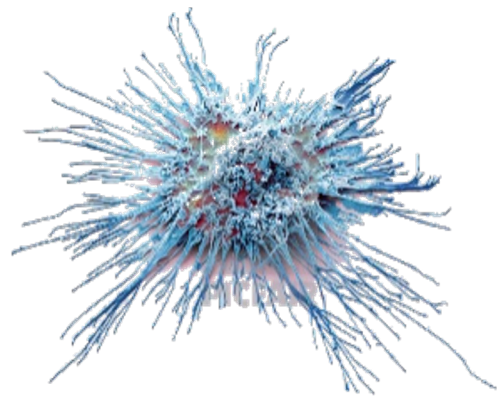


**Autoreactive T Cell
(in Patient)**



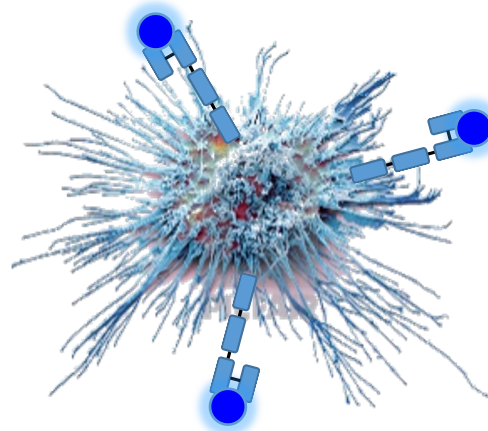
**Autoreactive B Cell
(in Patient)**

Example: Dendritic Cell / APC Vaccines

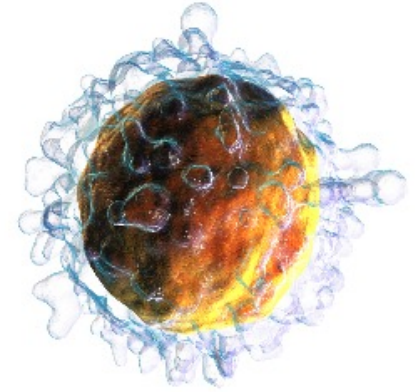


**Dendritic Cell
(from Patient)**

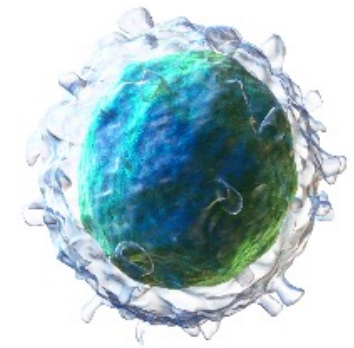
Auto-Ag
Conditioning



**Tolerizing DC
(Return to Patient)**

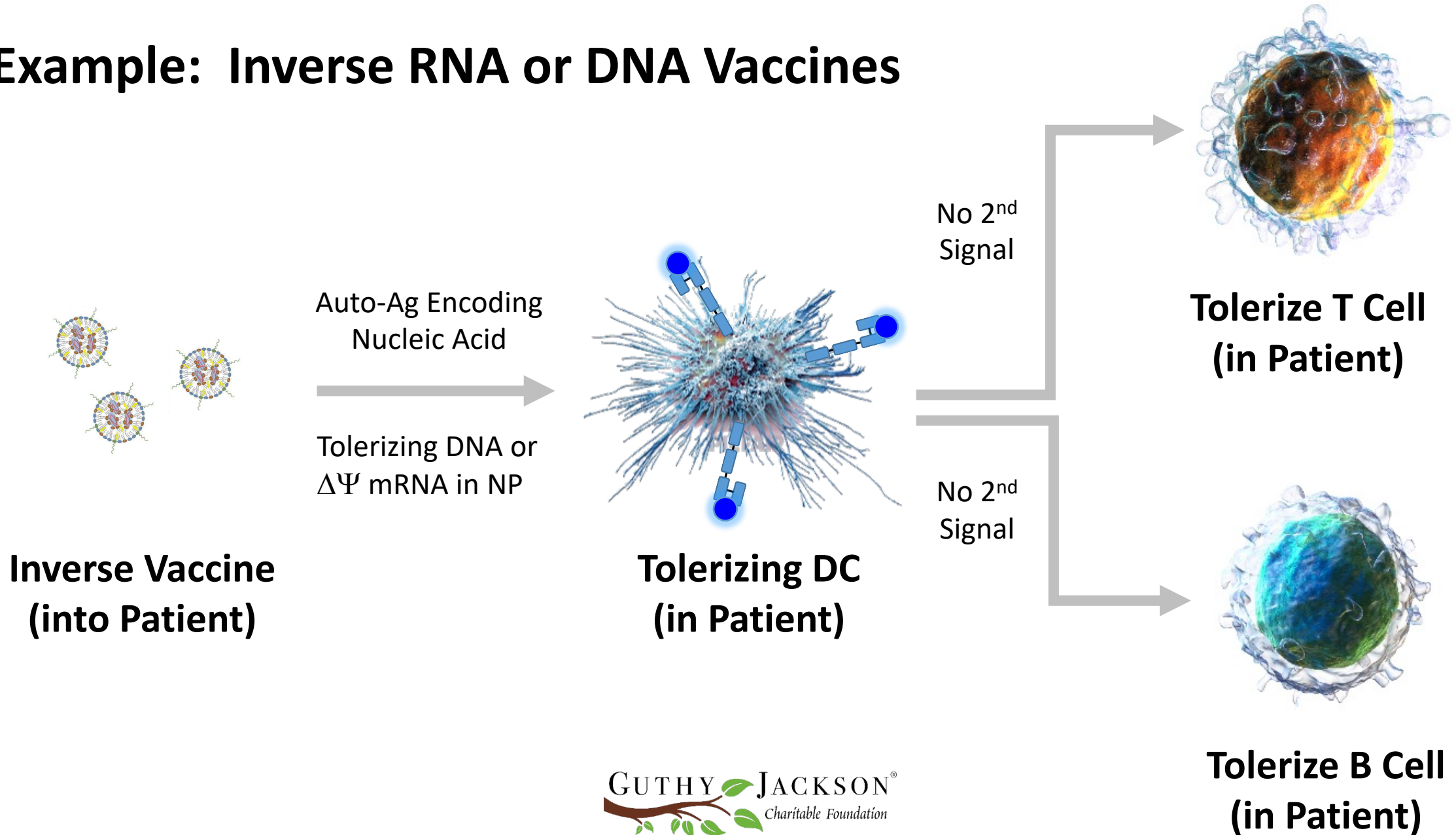


**Tolerize T Cell
(in Patient)**

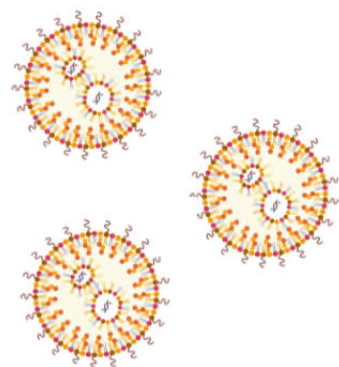


**Tolerize B Cell
(in Patient)**

Example: Inverse RNA or DNA Vaccines



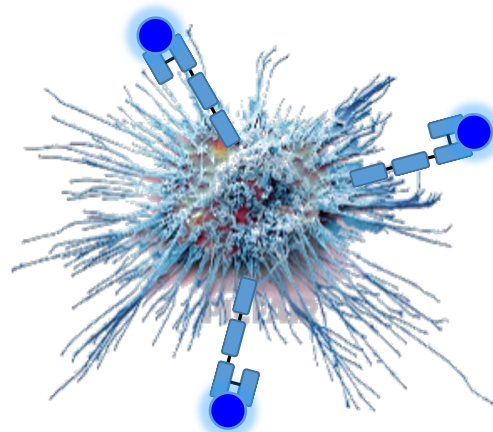
Example: Tolerigenic Nanoparticles



Tolerigenic Nanoparticle (into Patient)

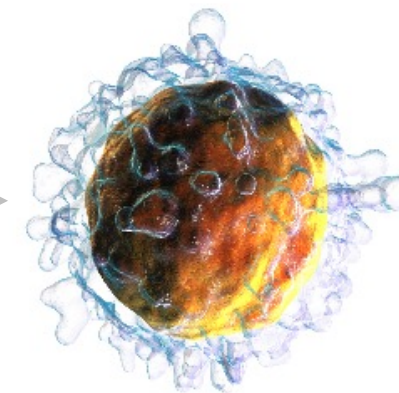
Autoantigen or Peptide

Tolerizing NP Formulation



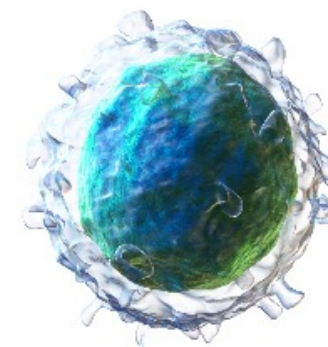
Tolerizing DC (in Patient)

No 2nd Signal



Tolerize T Cell (in Patient)

No 2nd Signal



Tolerize B Cell (in Patient)

Is Tolerization a Treatment or Cure ?



TREATMENT

Therapy that induces **temporary** immune tolerance to an auto-antigen
Occasional re-dosing may be needed; no need for immune suppression



CURE

Therapy that induces **permanent** immune tolerance to an auto-antigen
Re-dosing would be unnecessary; no need for immune suppression



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