

Heather Zwickey, PhD

Immunology Fundamentals and Current Updates



Outcomes

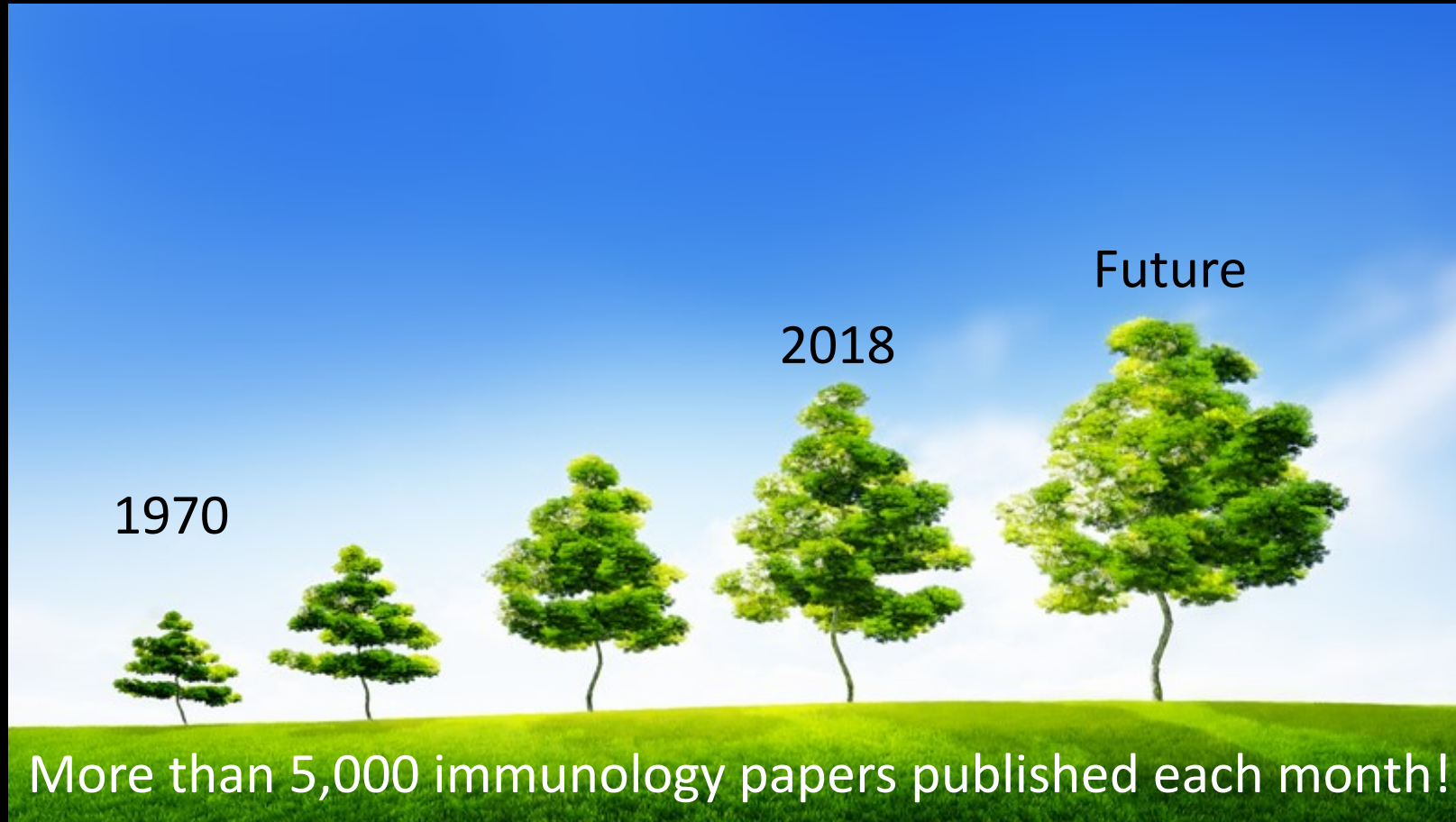
- Recall immunology terminology
- Describe the immune response to infectious disease
- Apply immunological principles to infectious disease – with respect to cytokine balance.



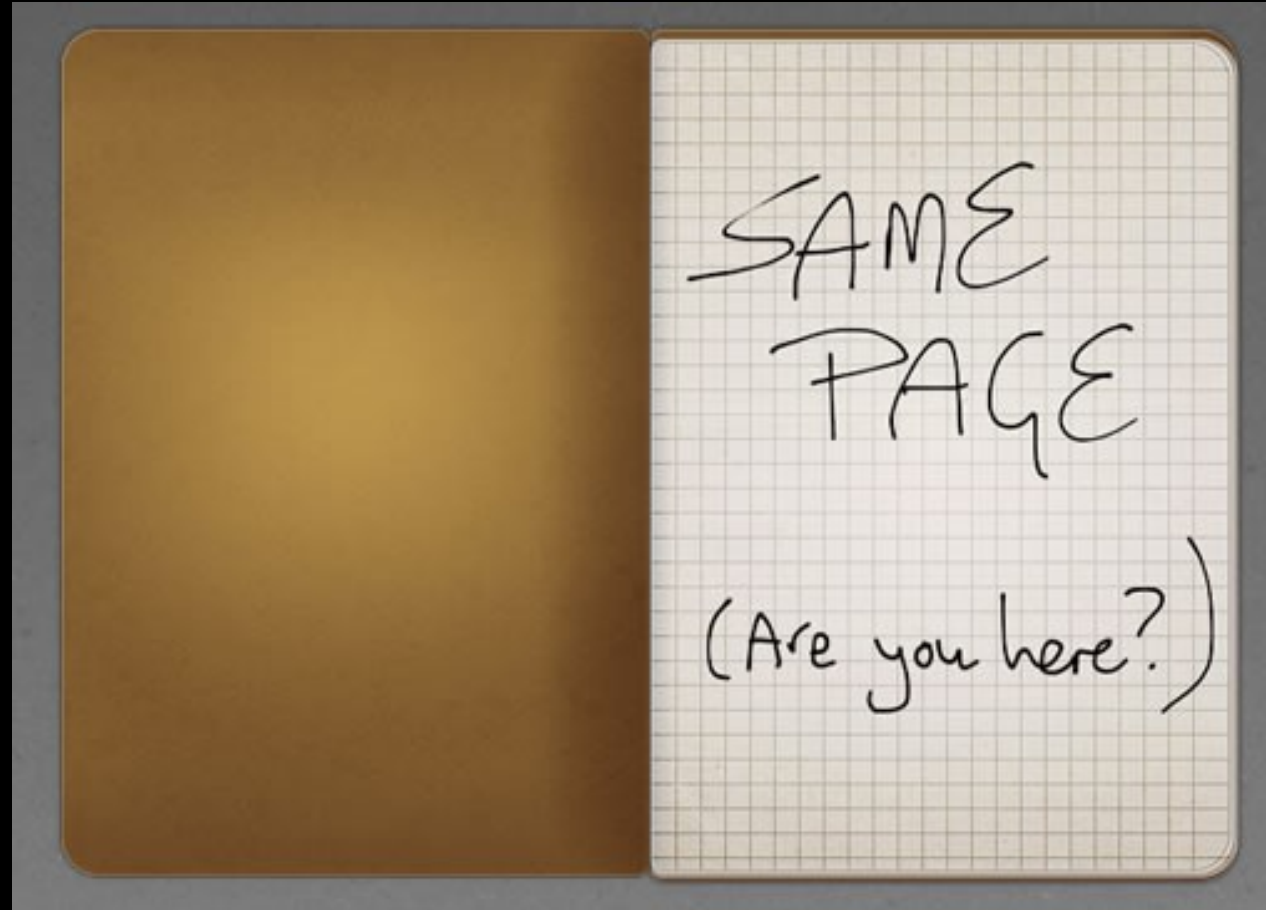
Depending on when you went to medical school...



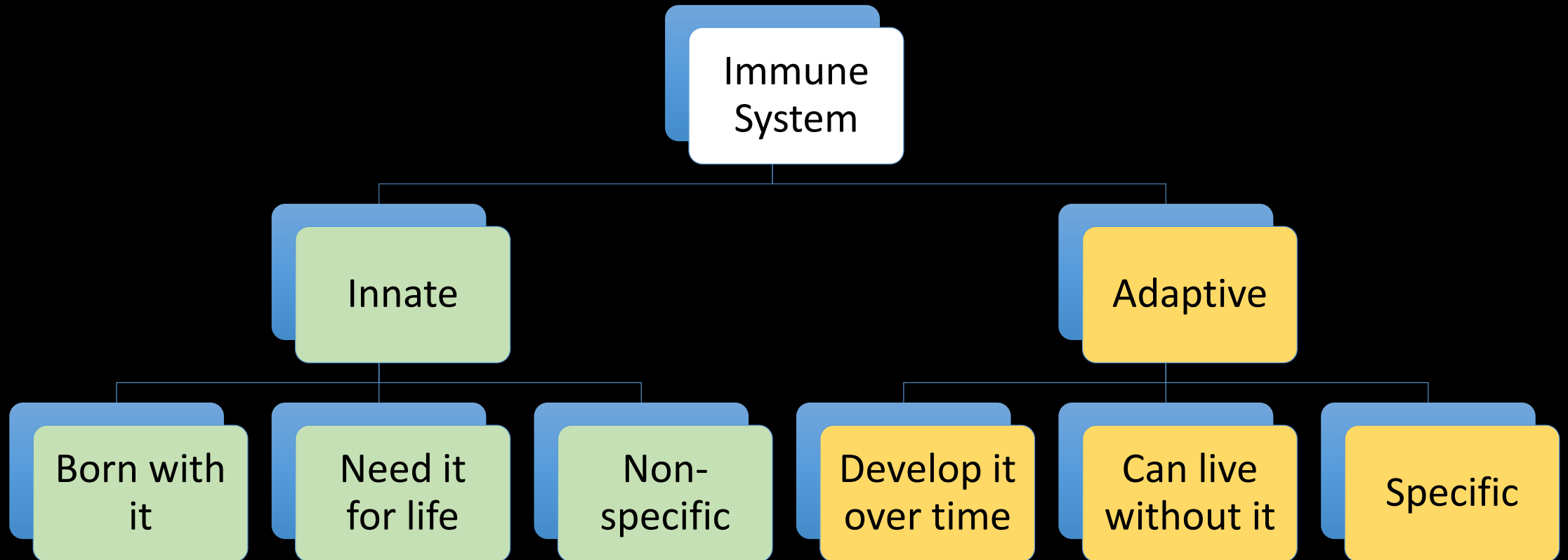
Immunology field is growing!



Immunology Review Goal



Innate vs Adaptive Immunity



Cells Involved

Innate	Adaptive
Macrophages	B Cells
Dendritic Cells	T Cells (CD4 and CD8)
Neutrophils	NKT Cells
Eosinophils	
Basophils	
Mast Cells	

How we identify cells

CD –
Cluster of
Differentiation



Cells Involved

Innate	Markers	Adaptive	Markers
Macrophages	CD11b	B Cells	CD19
Dendritic Cells	CD11c, MHC	T Cells	CD3 + CD4 or CD8
Neutrophils	CD15	NKT Cells	CD56 + CD3
Eosinophils	CD11b, CD193		
Basophils	2D7, CD123		
Mast Cells			

Types of Antigen



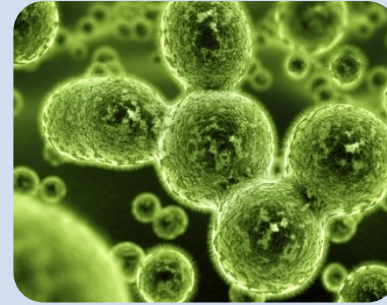
Bacteria
& Virus



Worms



Food



Mold

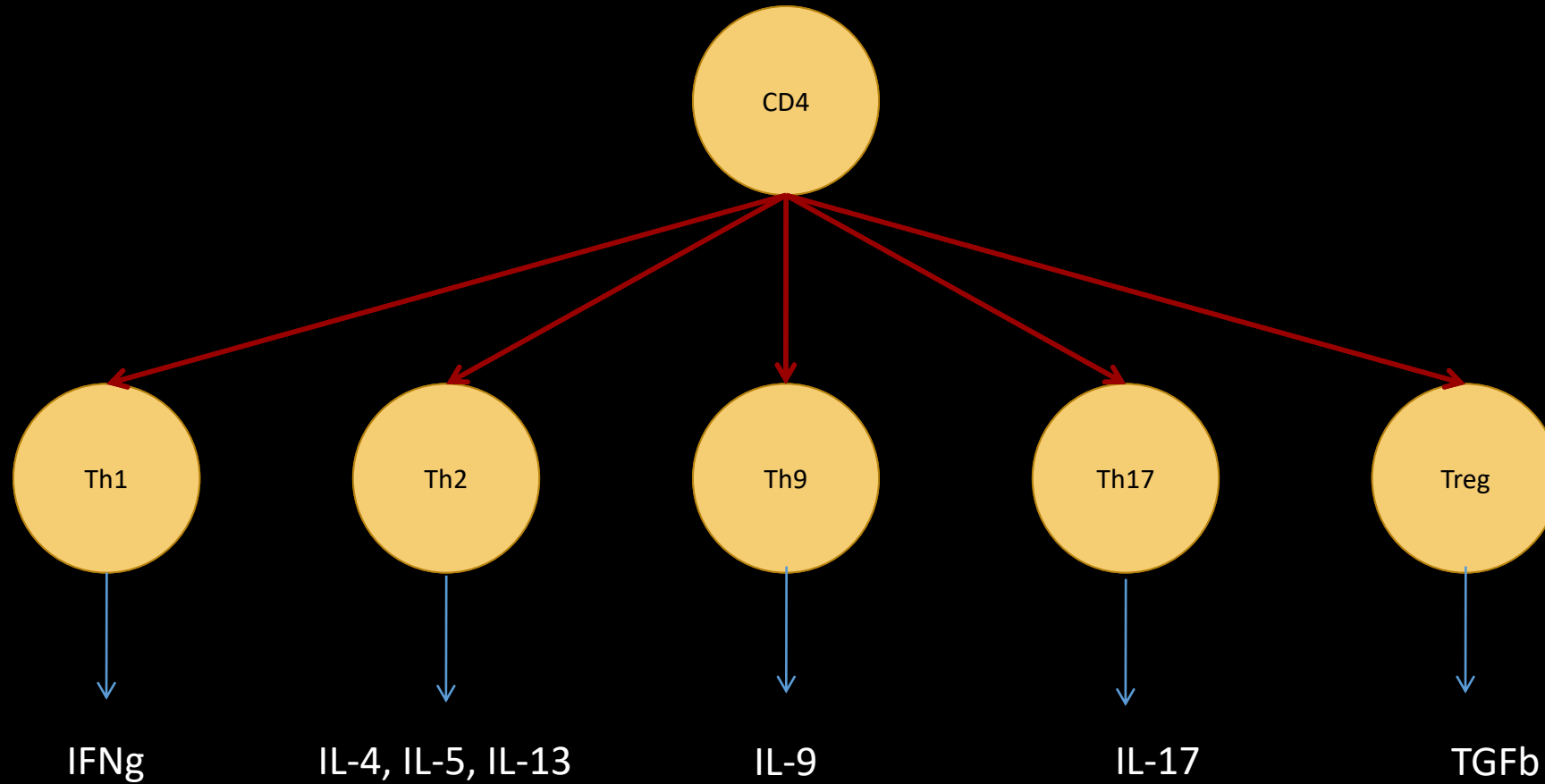


Self

Types of Immune Responses

Reactions	T Cell Response
Bacteria and Virus	Th1
Worms (some parasites)	Th2
Asthma	Th9
Fungi (some parasites and extracellular bacteria)	Th17
Food	Treg/Th3 *Dominant

CD4 T cell Subtypes

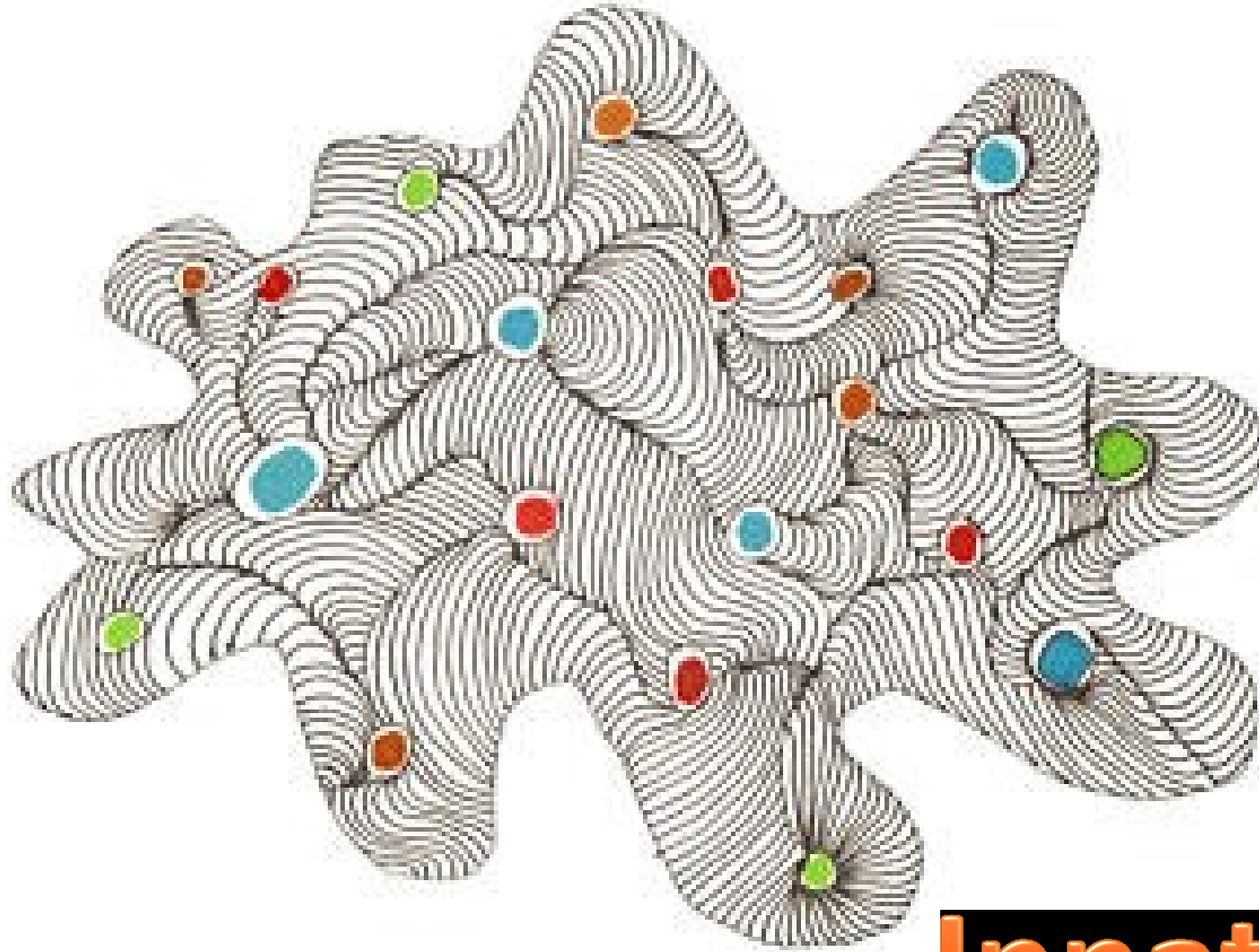


Immune Reaction Table

Reaction Type	T Cell Response	Cytokines	Antibodies
Bacteria/Virus	Th1	IFNgamma TNFalpha	IgG/IgA
Worms	Th2	IL-4, IL-5, IL-13	IgE
Fungus	Th17	IL-17, IL-23 *IL-6	IgG
Asthma	Th9	IL-9, IL-10	IgE
Food	Treg/Th3	TGFbeta, IL-10	IgA

Process Overview





Innate Immunity

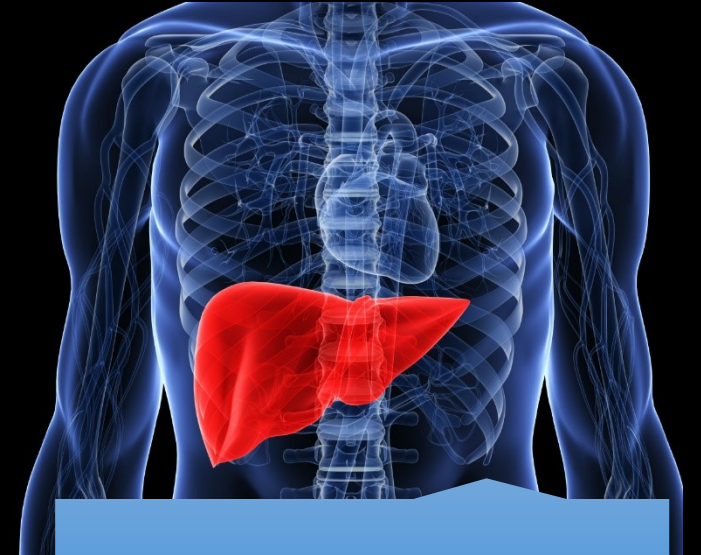
Tick Bite...



Deer tick bite



Cross physical
barrier



Activate proteins

Proteins



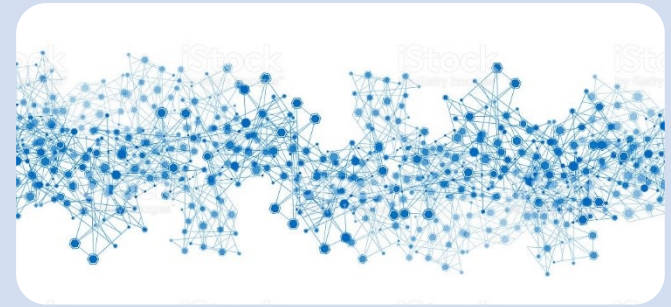
General

- Fibrinogen
- Habtoglobluin
- Serum amyloid protein
- Kinins



CRP

- hsCRP

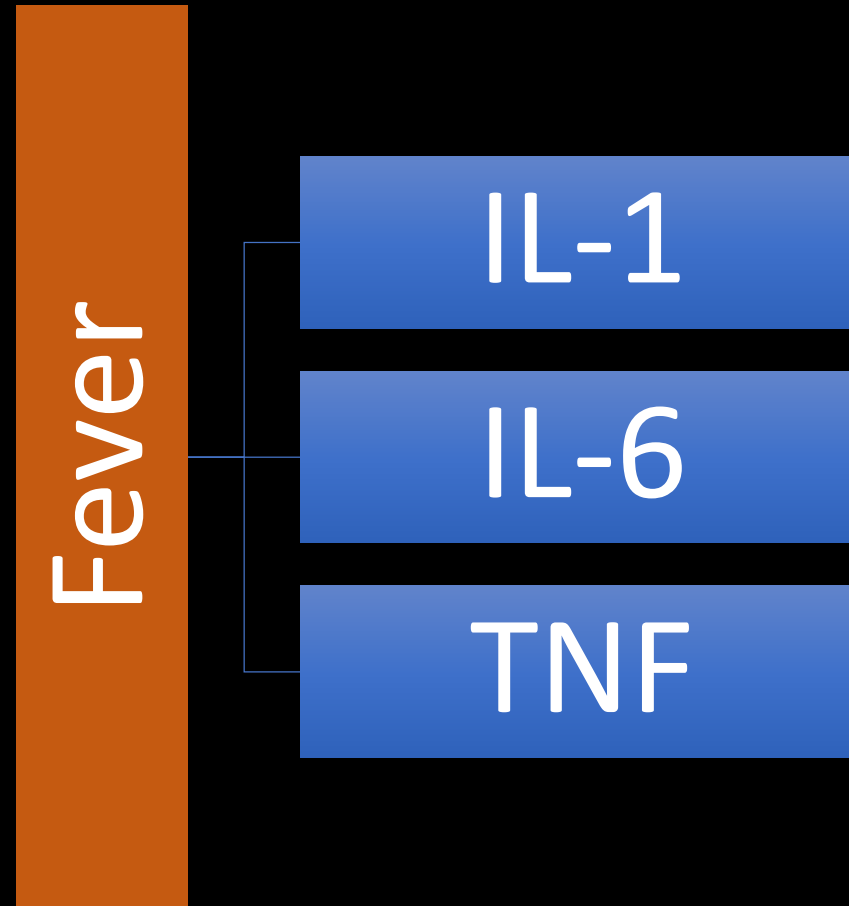


Cytokines

- IL-1
- IL-6
- TNF

Recall Systemic Inflammation

- Acute phase
 - Defensins
 - Kinins
 - Complement
- Innate phase
 - Inflammatory cytokines
 - Cellular response
 - Macrophages
 - Dendritic Cells
 - Neutrophils



Sickness Behavior



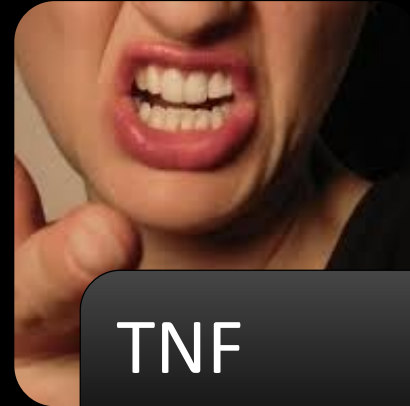
IL-1

- Depression



IL-6

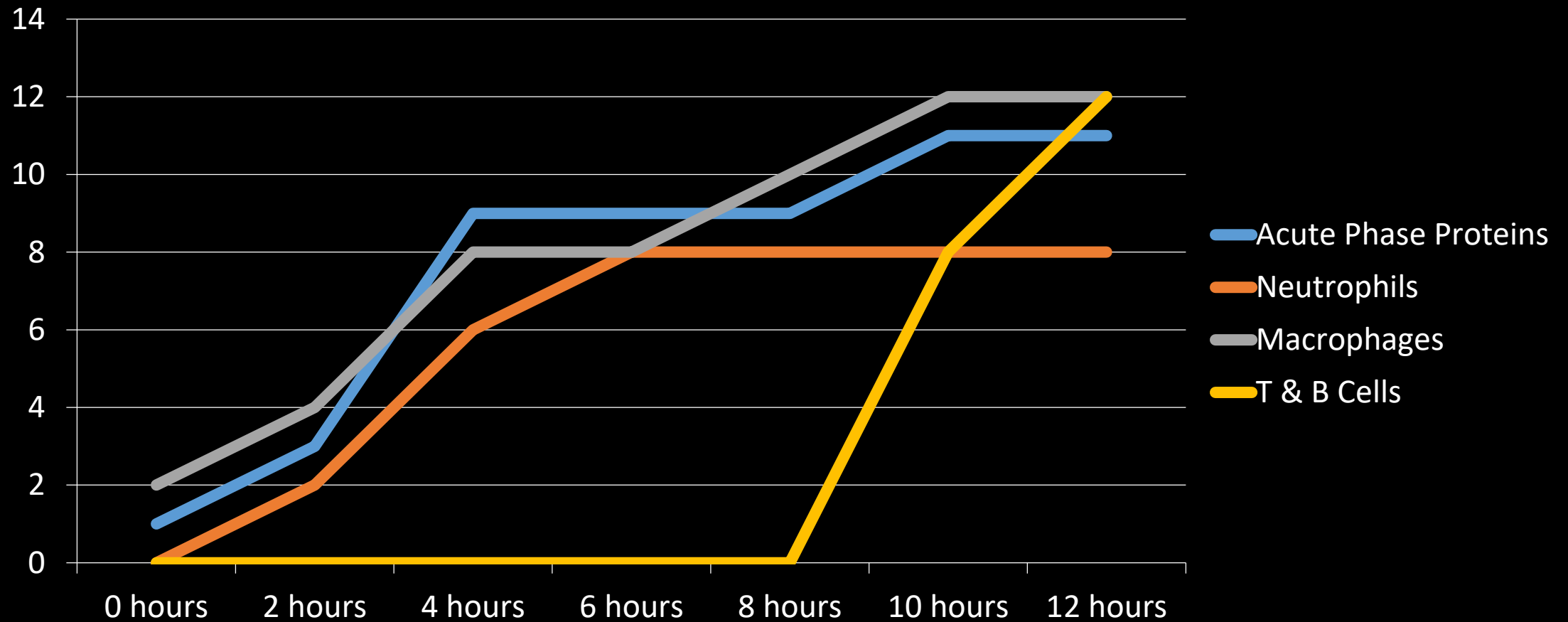
- Anxiety



TNF

- Hostility

Timing – Acute Phase through Innate Phase

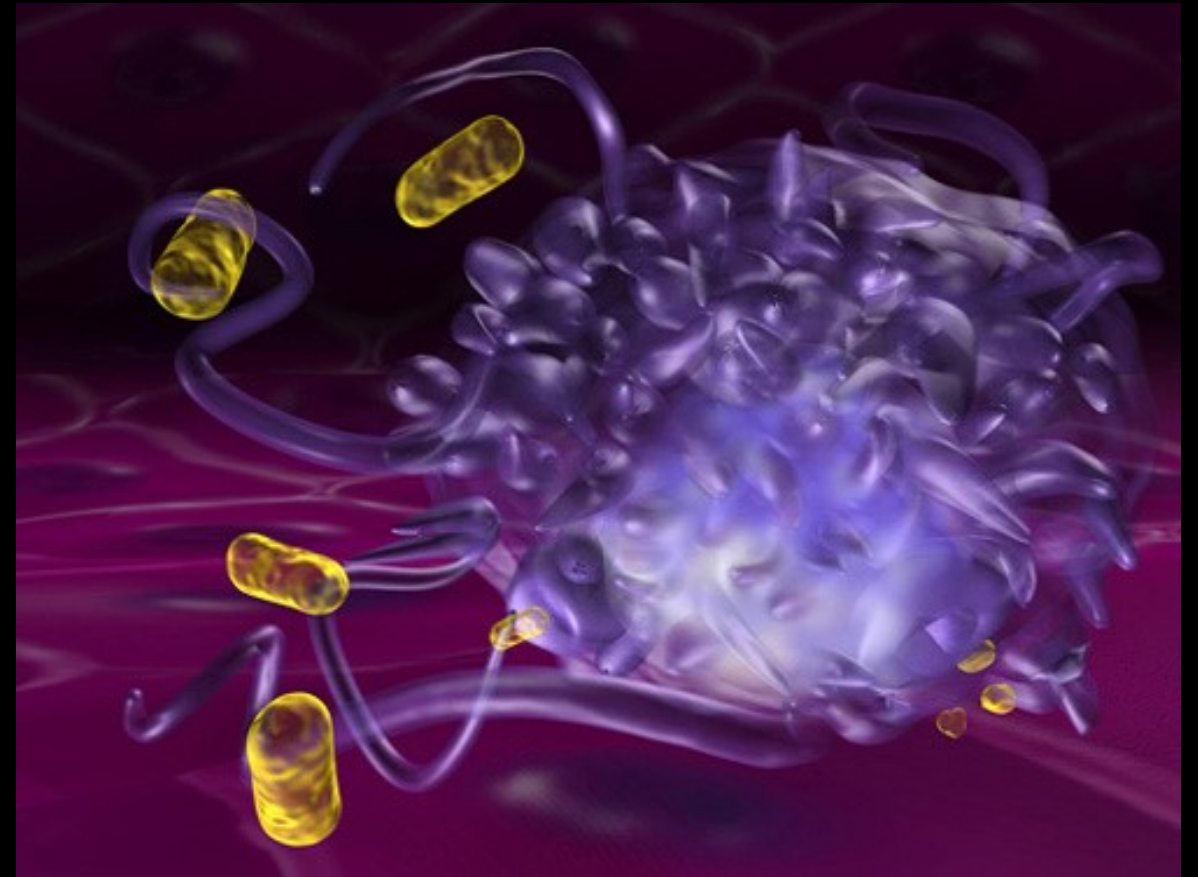


Innate Response

Macrophages and Dendritic Cells (DCs) phagocytose *Borrelia*

Macrophages and DCs carry the organism (antigen) to the draining lymph node

The neutrophils and acute phase proteins keep things in check until the specific immunity arrives.

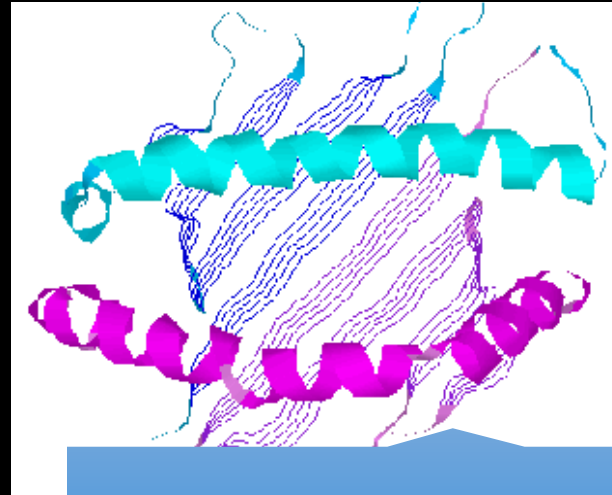


APCs

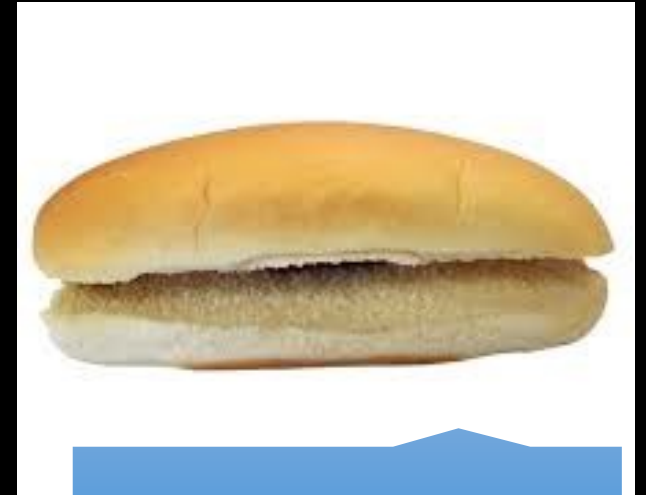
Antigen presenting cells

- Macrophage
- Dendritic cell (DC)
- B cell

Chops up antigen and puts it in the MHC molecule



MHC



Hot Dog in Bun

Antigen Presentation

MHC Class II

Extracellular (exogenous) antigen
Stimulates CD4 T cells
(Thelpers-Th)

HLA – DP

HLA – DQ

HLA –DR

MHC Class I

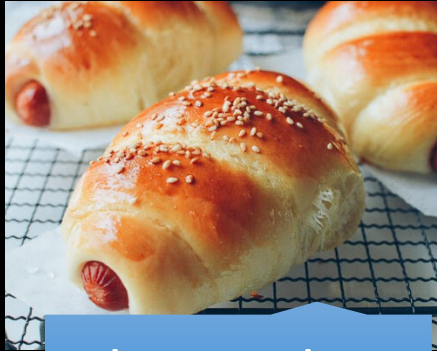
Intracellular (endogenous) antigen
Stimulates CD8 T cells
(Tkillers-CTL)

HLA – A

HLA – B

HLA – C

Thousands of MHC Haplotypes



Chinese bun



Mini bun



Poppyseed



Pretzel



Race car



Paleo



Brioche bun

Antigenic Variation



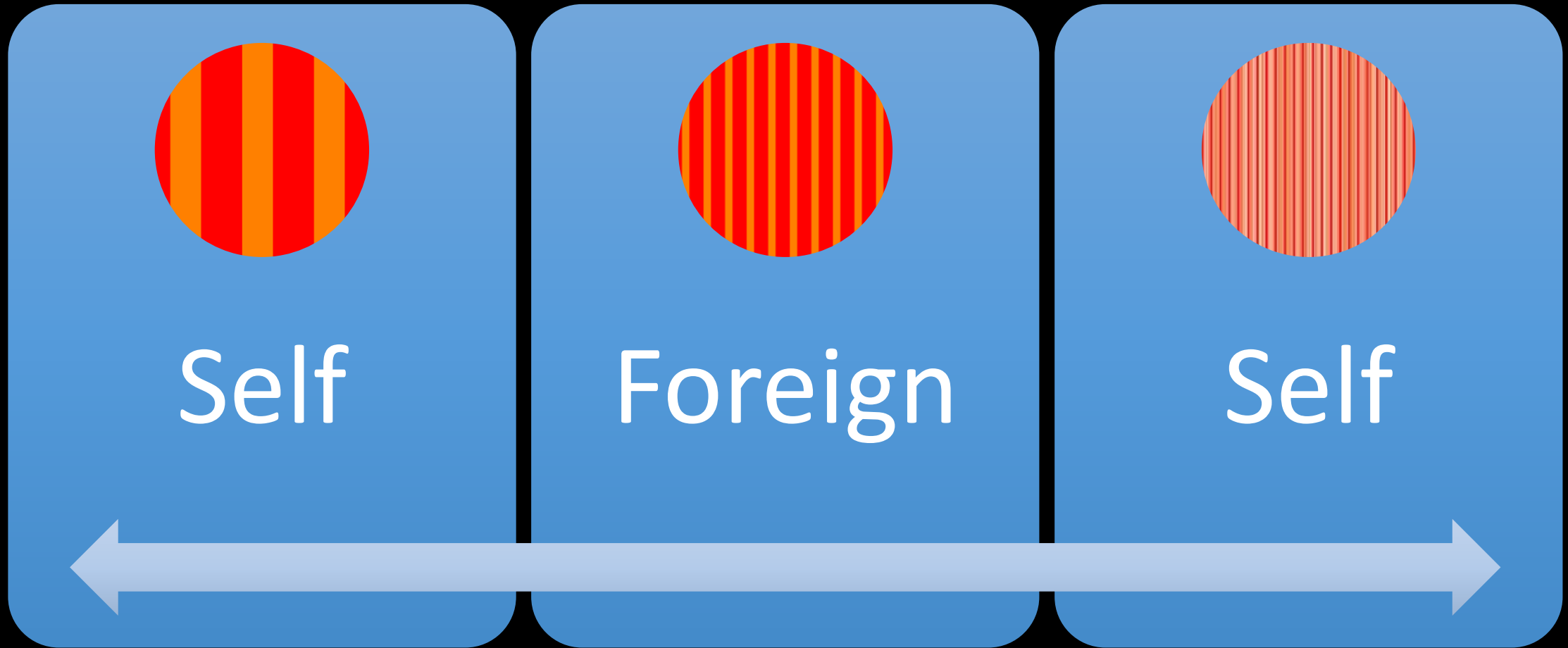
Change in the
antigen...



...means it may no
longer fit in the
MHC

Therefore, T cells may no longer respond or antibodies may no longer bind to it.

Molecular Mimicry



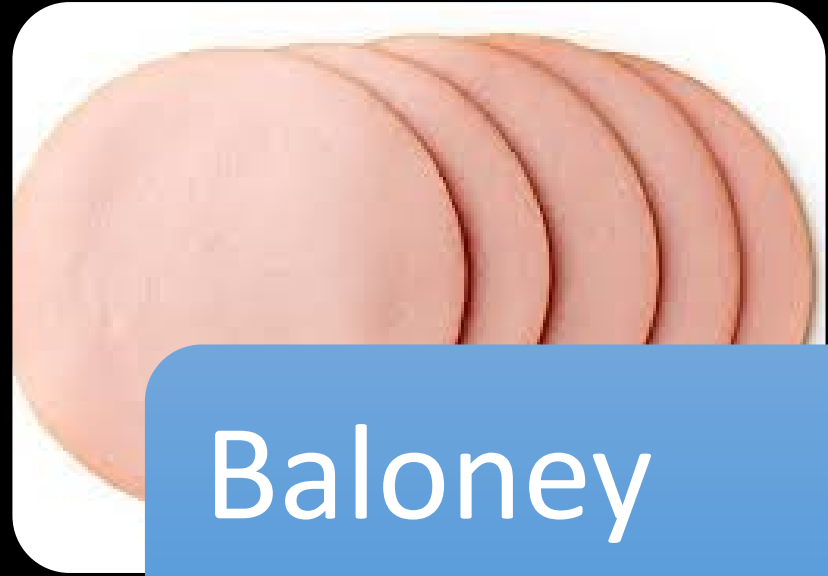
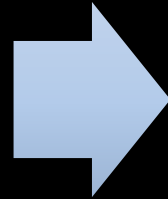
Therefore, when attacking foreign antigen, self antigen may also be attacked, causing autoimmunity.

Epitope Spreading



Hot Dog

- Initial response

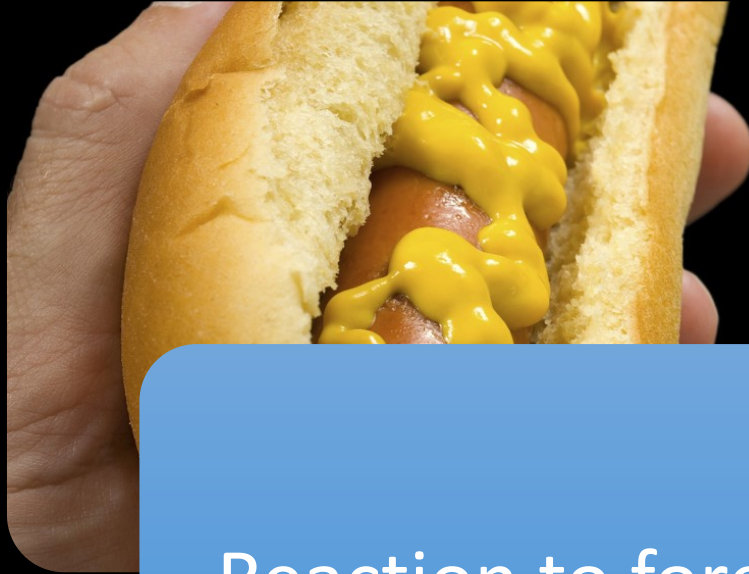


Baloney

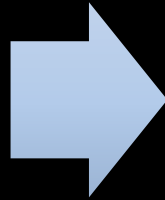
- Similar antigen

As response continues, new hidden or cryptic antigens are targeted.

Bystander Activation



Reaction to foreign
antigen



Simultaneous
reaction to self
antigen on same cell

- Leads to autoimmunity

Borrelia burgdorferi



- Microbe has 5 oligopeptide binding proteins
- Implications: Limited number of peptides to bind to HLA molecules
- Likely binds to specific HLAs
 - Some people will be more susceptible than others

Groshong AM, Dey A, Bezsonova I, Caimano MJ, Radolf JD. Peptide Uptake Is Essential for *Borrelia burgdorferi* Viability and Involves Structural and Regulatory Complexity of its Oligopeptide Transporter. *mBio*. 2017;8(6):e02047-17. doi:10.1128/mBio.02047-17.

Co-infection (2-15%)

B. burgdorfi



A.
phagocytophilum

B. burgdorfi



Babesia microti

Pattern Recognition Receptors: PRRs & TLRs



Pattern Recognition Receptors (PRR)

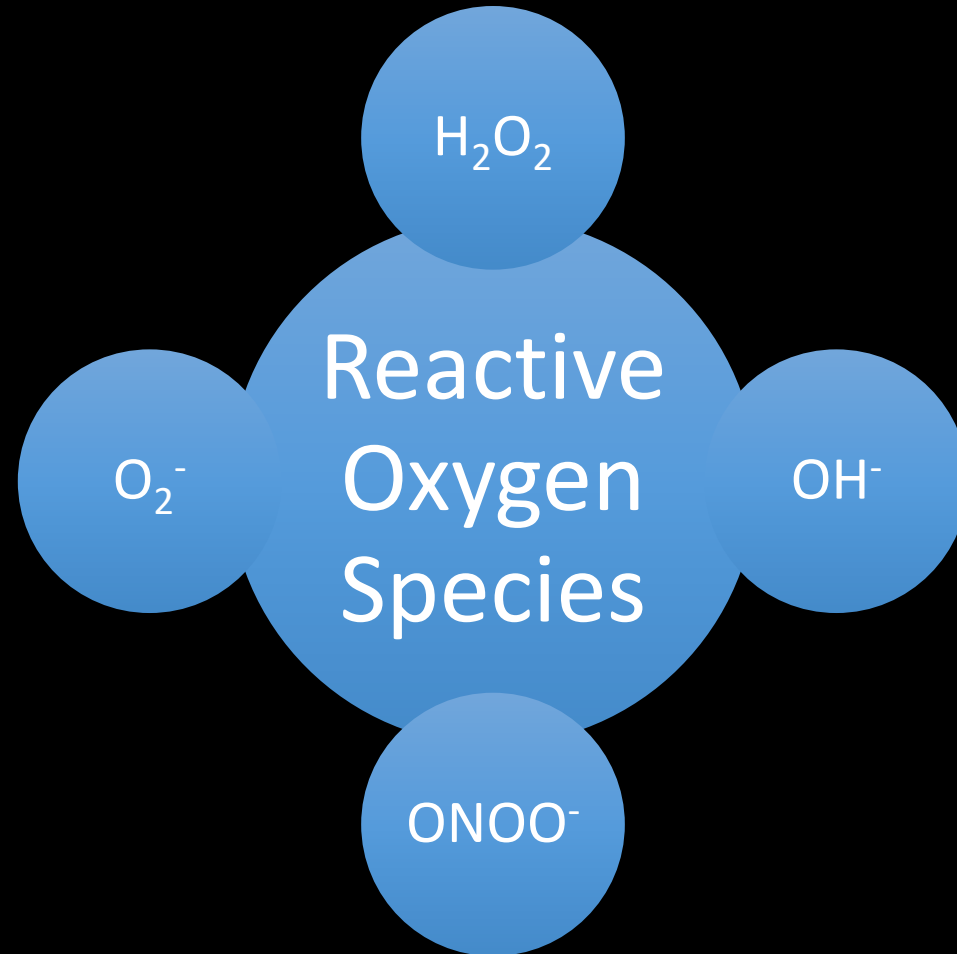
- On macrophages, DCs, Neutrophils
- Recognize bacterial and viral proteins as dangerous



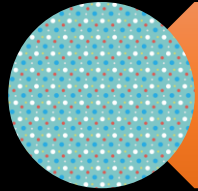
Toll Like Receptors (TLR)

- Subset of PRRs
- Stimulation leads to “danger” response

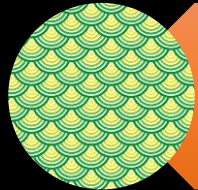
Danger signal leads to...



Immunological Danger



Reactive Oxygen Species



Leukotrienes and Prostaglandins



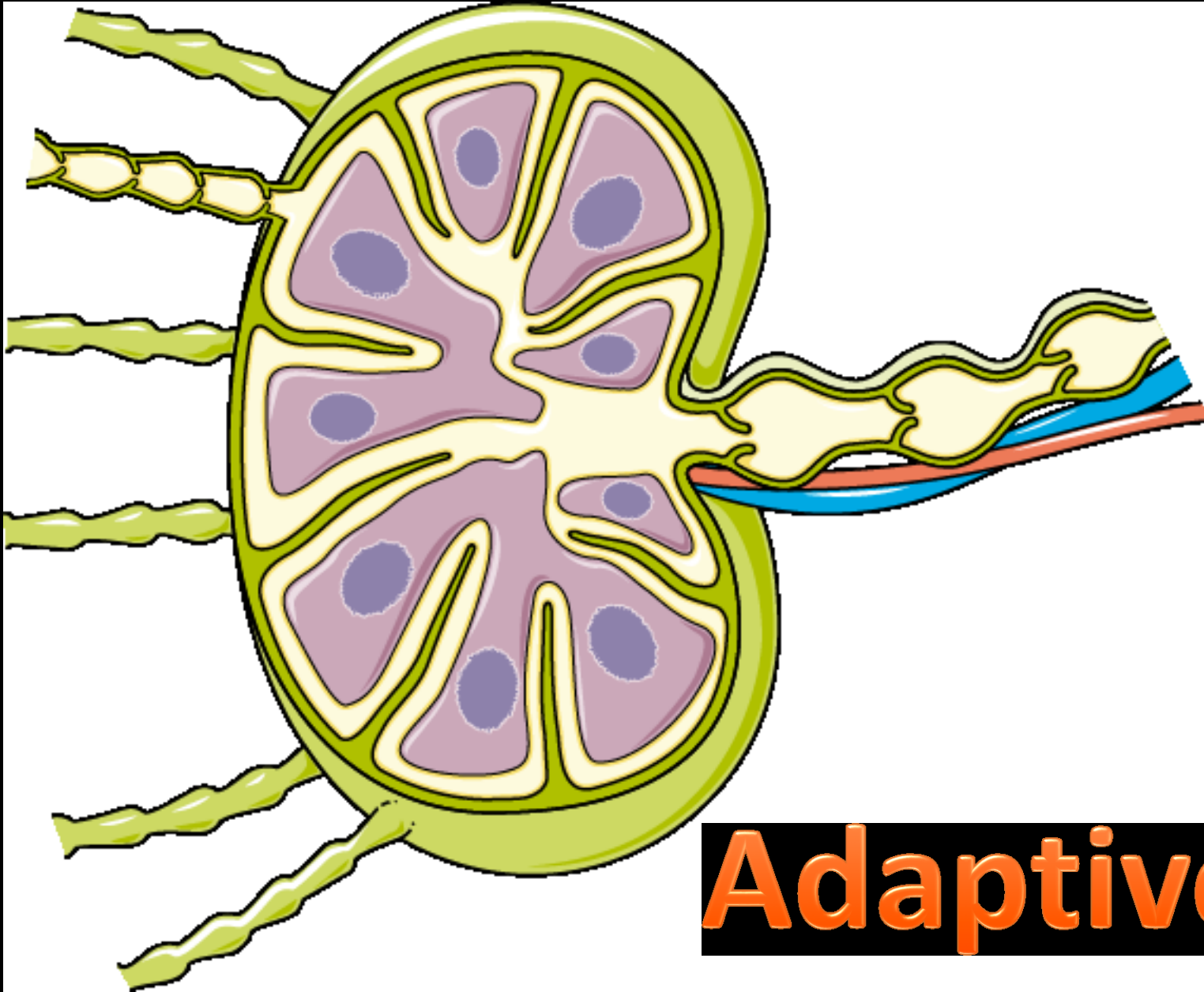
Costimulatory Molecules (CD86)



Cytokines

Mini-Quiz

1. Which cytokine makes people tired and malaised?
2. Which cell types will be the first to phagocytose *Borrelia*? (There are 3.)
3. Which proteins tell the cell that an infection has occurred?



Adaptive Immunity

Where we're at...

- It's 4-8 hours post infection
- Macrophages and DCs are at the lymph node
 - They have antigen in their MHC molecules
 - They're activated
 - They're making ROS
 - Some are dying and releasing microbes in the lymph node
 - Some are waiting for B and T cells to help activate them
- Where are the B and T cells?

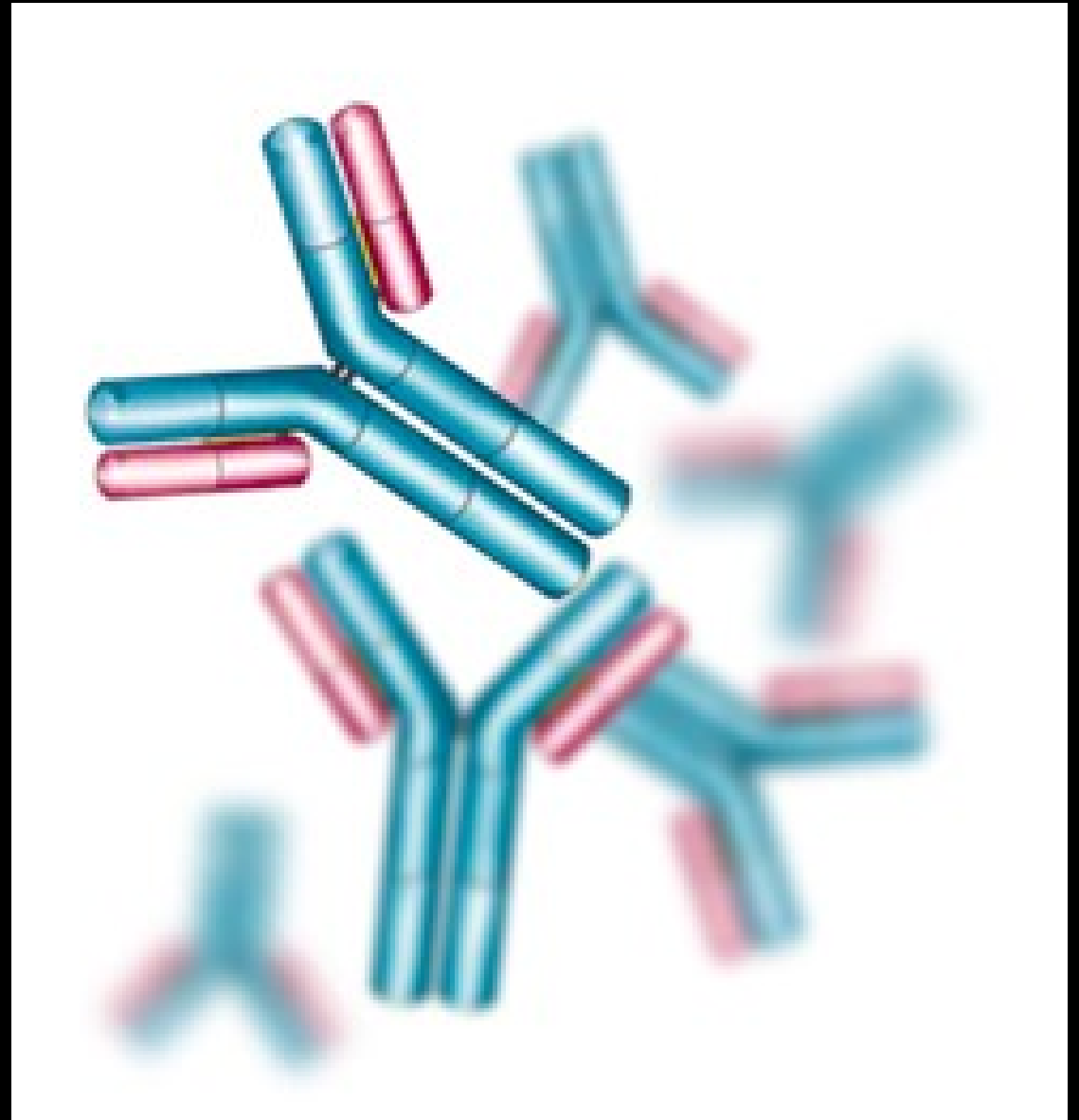
B cells

B cells make antibodies

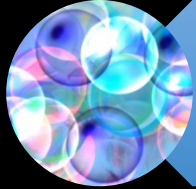
You already have antibodies specific for anything you may encounter one day.

Exposure to antigen increases the number of antibodies, 100–1000 fold.

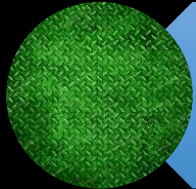
IgM, IgD, IgG, IgE, and IgA



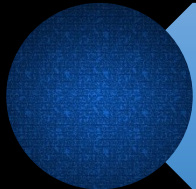
Antibody Function



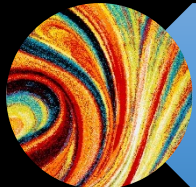
Opsonization



Neutralization

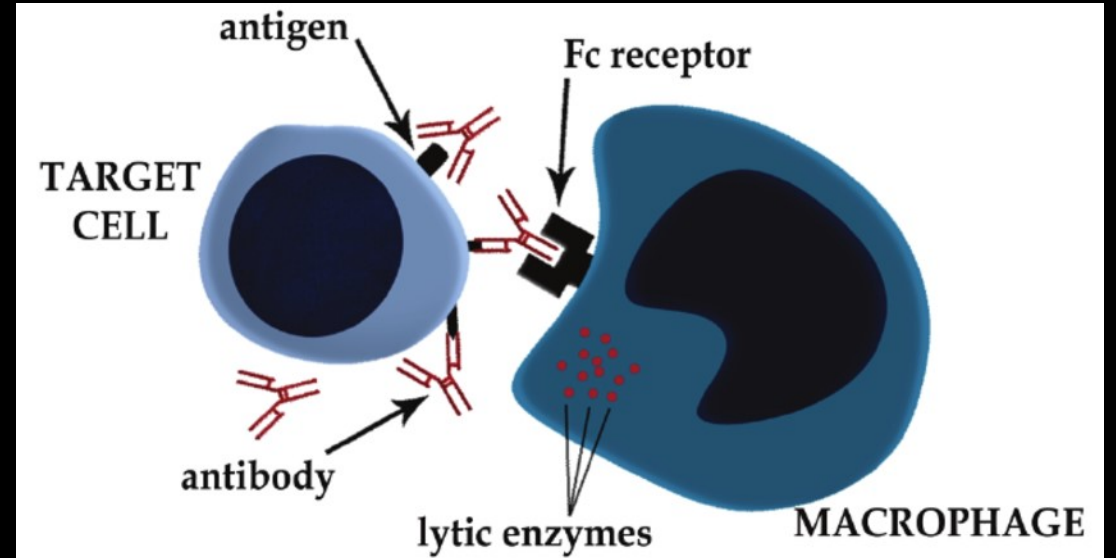


ADCC



Fc Receptor

Antibodies are adapters

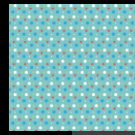


Antibody Isotypes



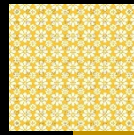
IgM

- Made first
- Indicates recent infection



IgD

- ???
- Rhogam



IgG

- Made to bacteria and virus
- Highest level in blood
- Half-life of 23 days
- Th1 response



IgE

- Made to worms and parasites
- Mast cell
- Allergies
- Half-life of 2 days
- Th2 response



IgA

- Made to Food
- Found in secretions
- Tolerance
- First antibody - saliva
- Treg response

Antibody Details

	Antibody	Characteristics	Location	Cytokine for Switch
	IgM	Pentameric Made first High concentration means recent infection Can be made at 5 months of gestation ½ life = 2-7 days	Blood	IL-2
	IgD	Monomeric Unknown function ½ life = 3 days	Blood	Unknown
Best for infections	IgG	Monomeric Highest level in serum Can cross the placenta (passive immunity) Associated with a Th1 response ½ life = 23 days	Blood	IFN γ
	IgE	Monomeric Response to parasites Involved in allergies Associated with a Th2 response ½ life = 2 days	Blood	IL-4
Protection from Breast milk	IgA	Monomeric or Dimeric, Found in secretions—Breast Milk Import role in infections—first Ab encountered Associated with Th3 response Can also be Th1 - for mucosal pathogens ½ life = 3 days	Saliva, Breast milk, Secretions, Gut, Tears, Vaginal fluid	TGF β

Antibody response

Macrophages release Borrelia antigen in lymph node



```
graph TD; A[Macrophages release Borrelia antigen in lymph node] --> B[One B cell specific for antigen activated – Monoclonal activation]; B --> C[Antibodies bind – isotype is T cell dependent]; C --> D[Antigen cleared];
```

The diagram illustrates the antibody response process through a series of four steps, each in a colored box. The boxes are arranged in a descending staircase pattern from top-left to bottom-right. The first box is orange, the second is grey, the third is blue, and the fourth is green. Downward-pointing arrows connect the boxes: a pink arrow from the orange box to the grey box, a white arrow from the grey box to the blue box, and a yellow arrow from the blue box to the green box.

One B cell specific for antigen activated –
Monoclonal activation

Antibodies bind – isotype is T cell dependent

Antigen cleared

Polyclonal antibody response

Macrophages release Borrelia antigen in lymph node



```
graph TD; A[Macrophages release Borrelia antigen in lymph node] --> B[Many B cells specific for Borrelia antigens activated – Polyclonal activation]; B --> C[Antibodies bind – isotype is T cell dependent]; C --> D[Antigen cleared. More ideal response because many antigens attacked simultaneously.];
```

The diagram is a vertical flowchart with four colored rectangular boxes connected by downward-pointing arrows. The boxes are yellow, green, teal, and blue, each containing a step in the process of a polyclonal antibody response.

Many B cells specific for Borrelia antigens activated
– Polyclonal activation

Antibodies bind – isotype is T cell dependent

Antigen cleared. More ideal response because many antigens attacked simultaneously.

T cells

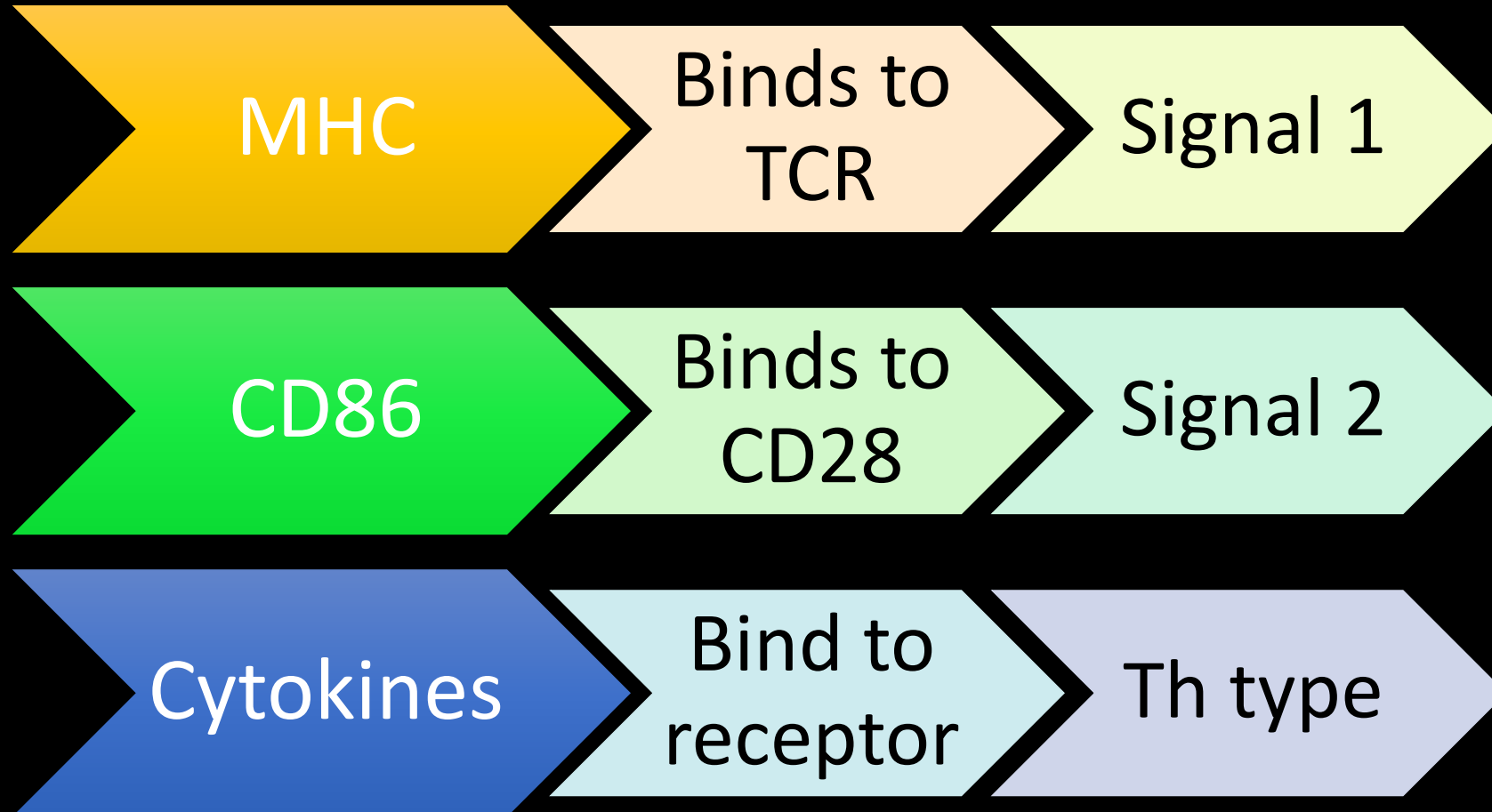
CD4 T cells make cytokines in response to a specific antigen.

CD8 T cells kill the cell displaying the specific antigen.

It takes 2 signals to activate a T cell.



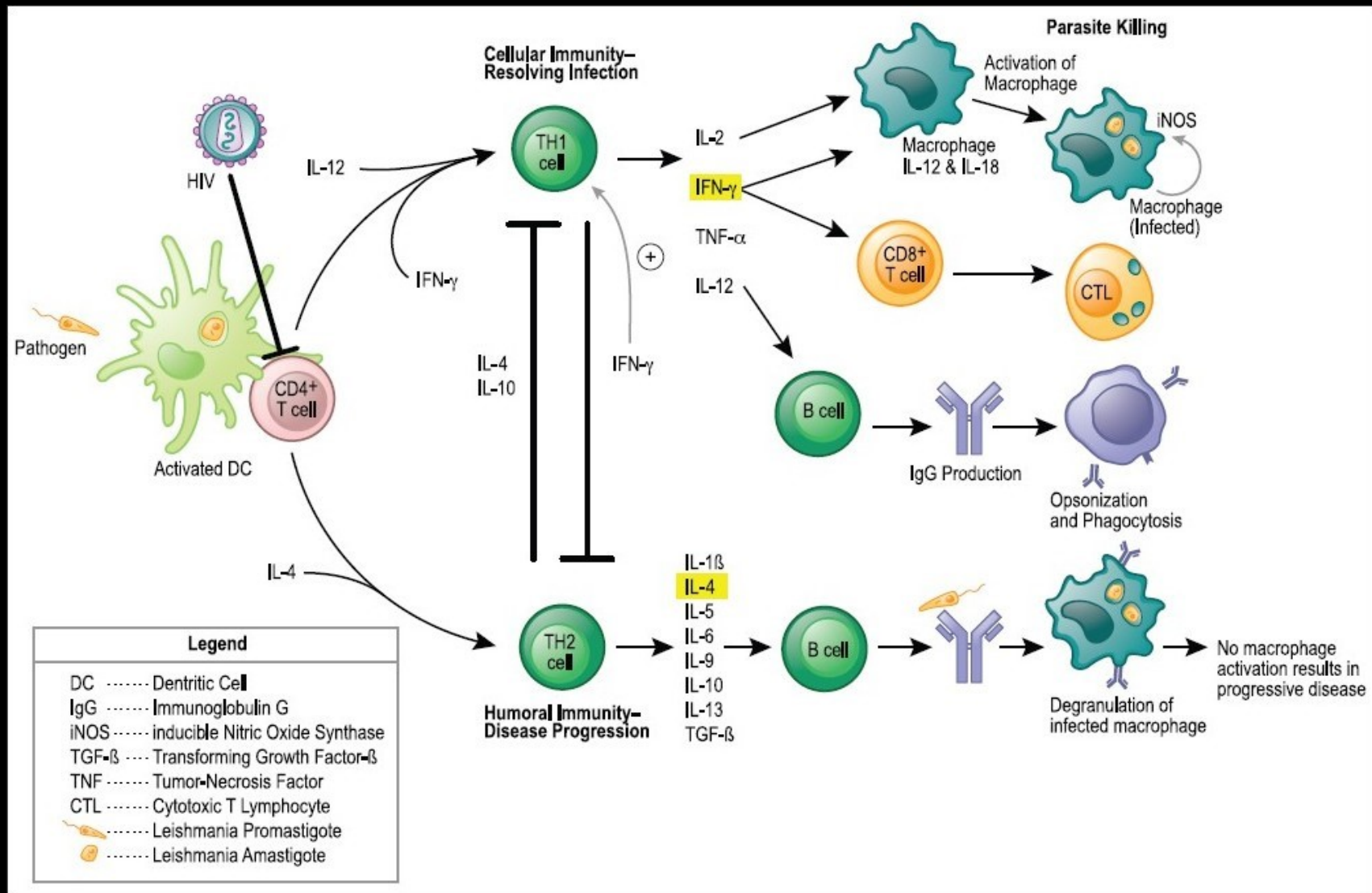
T cell activation



Overview of Immune Response

Overview of Immune Response				
APC	Makes cytokine	Triggers	CD4 T cells make:	B cells make:
DC	IL-12	Th1	IFN γ	IgG
DC	IL-4	Th2	IL-4, IL5, IL-13	IgE
DC	IL-4 + TGF β	Th9	IL-9, IL-10	IgE
DC	IL-23	Th17	IL-17	IgG
DC	IL-10	Treg/ Th3	TGF β	IgA

Cytokines tell the T cell what type of response to initiate



Th1/Th2

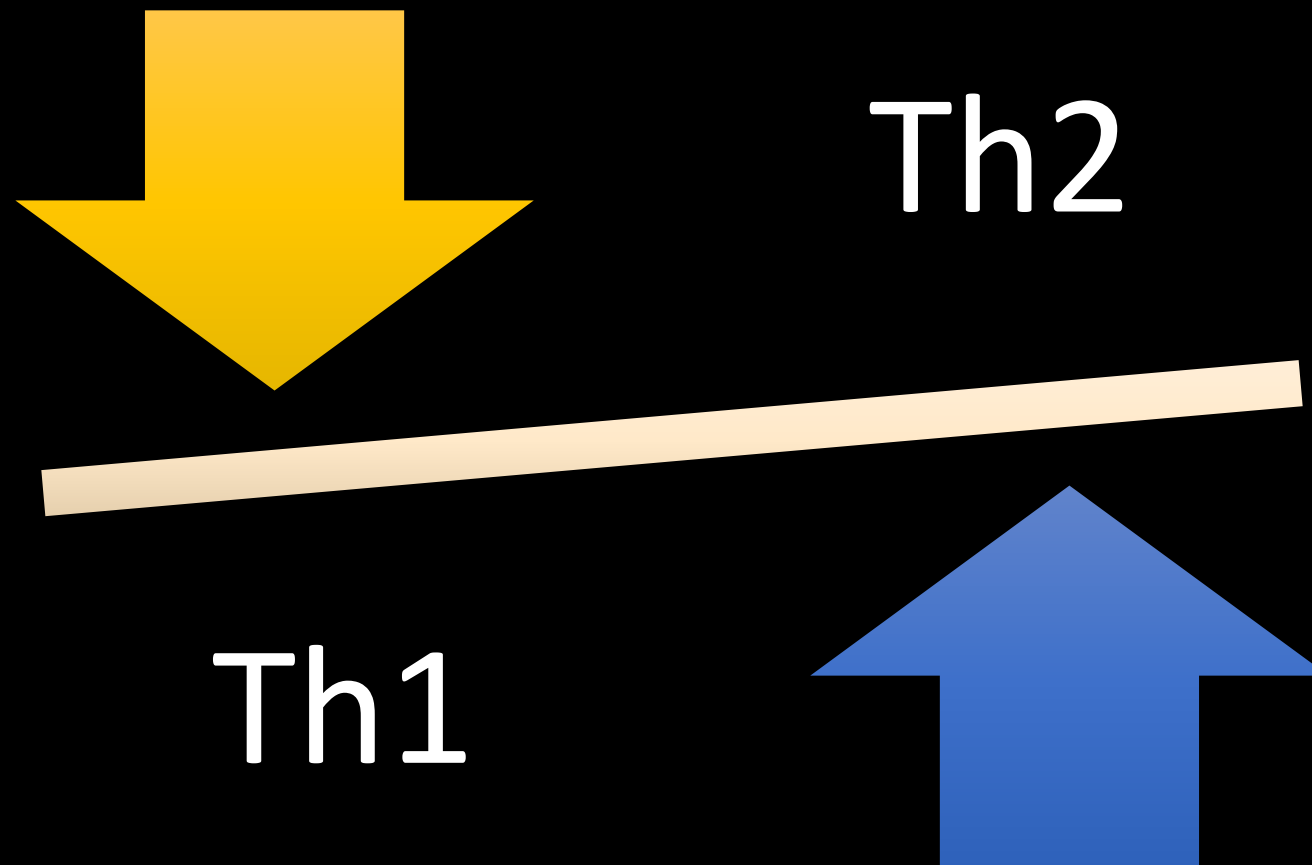
Th1/Th2 – Balance

If Th2 is high, it shuts down Th1 and vice versa.

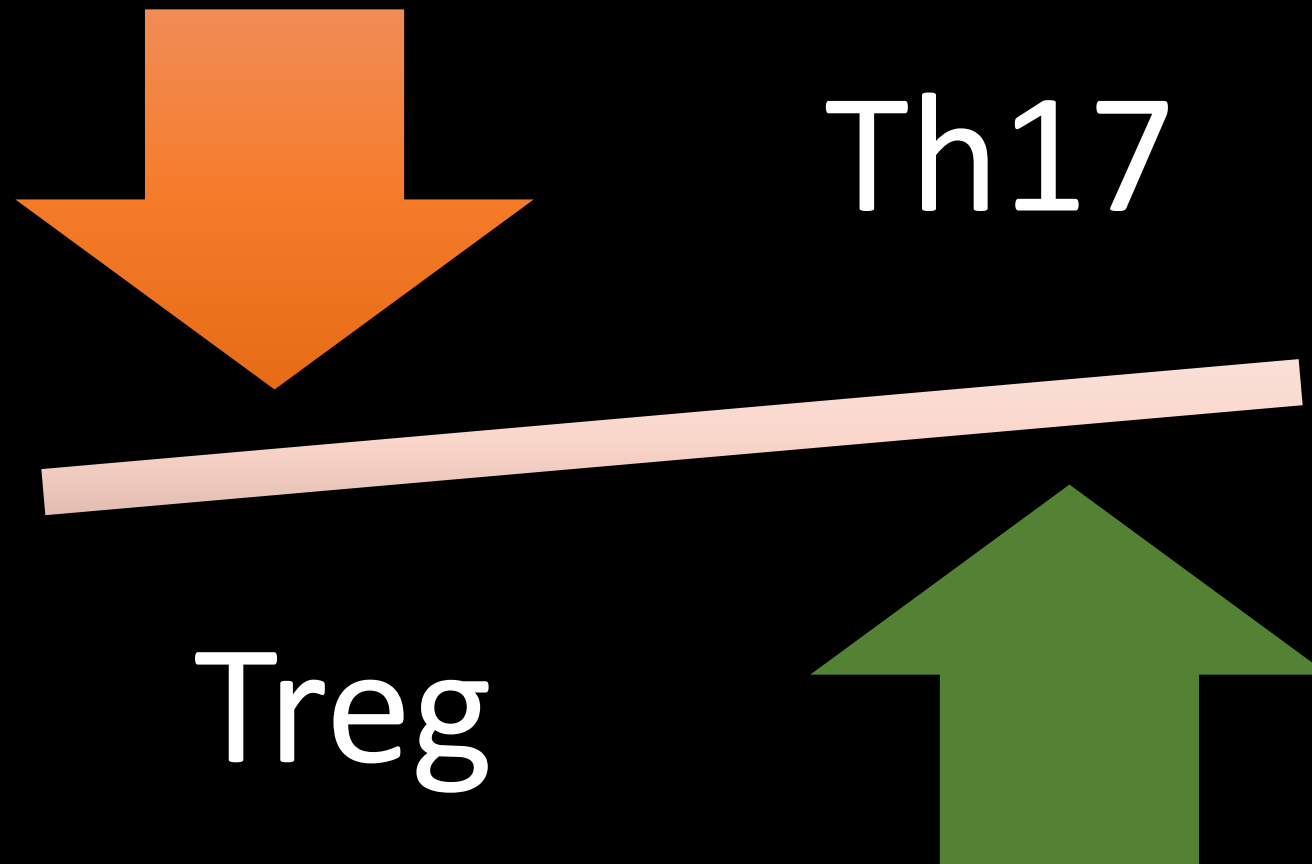
The genes are regulated so that you don't make both responses at the same time.



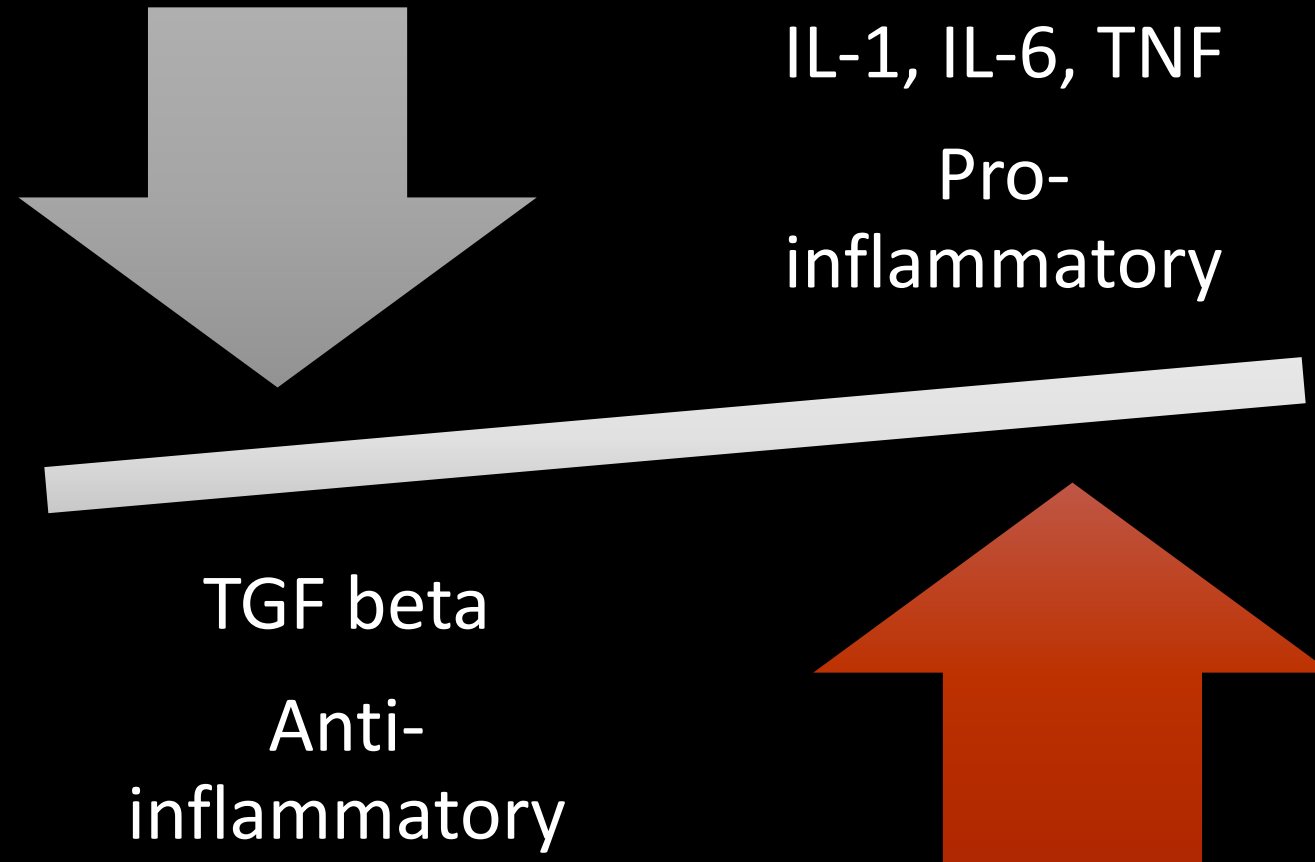
Balance



Balance



Balance



Manipulating cytokines can be therapeutic



Herbs

- Can drive Th1
- Can drive Th2



Probiotics

- Can drive Th1
- Can drive Treg

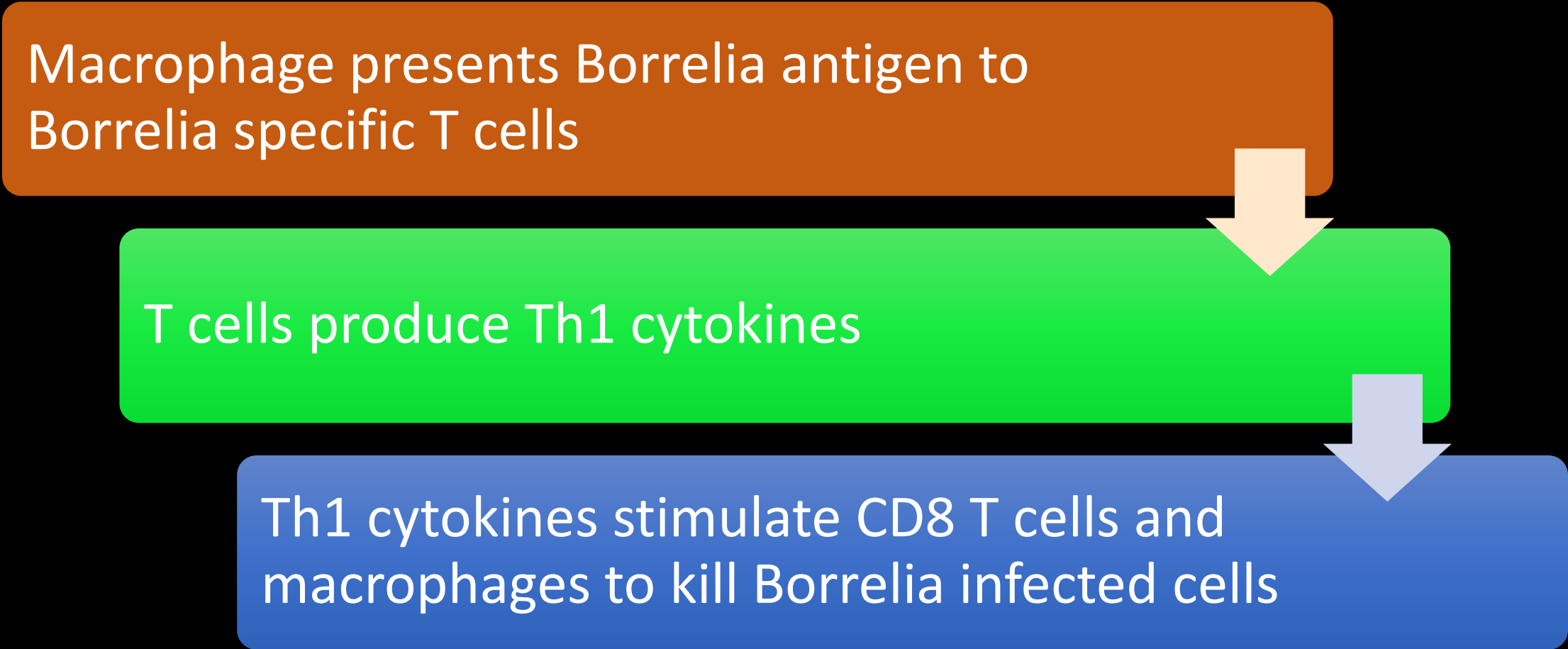


Meditation / Mindfulness

- Can drive Treg

T cell Response

Macrophage presents Borrelia antigen to Borrelia specific T cells



```
graph TD; A[Macrophage presents Borrelia antigen to Borrelia specific T cells] --> B[T cells produce Th1 cytokines]; B --> C[Th1 cytokines stimulate CD8 T cells and macrophages to kill Borrelia infected cells];
```

The diagram is a vertical flowchart with three colored rectangular boxes. The top box is orange and contains the text 'Macrophage presents Borrelia antigen to Borrelia specific T cells'. An orange arrow points down from the bottom right of this box to the top right of the middle box. The middle box is green and contains the text 'T cells produce Th1 cytokines'. A light blue arrow points down from the bottom right of this box to the top right of the bottom box. The bottom box is blue and contains the text 'Th1 cytokines stimulate CD8 T cells and macrophages to kill Borrelia infected cells'.

T cells produce Th1 cytokines

Th1 cytokines stimulate CD8 T cells and macrophages to kill Borrelia infected cells

Herb and Cytokines

	Herbs	Cytokines elicited	Ref
Increase Th1	Astragalus Oregon Grape	Increases IFNg & IL-2 Increases IL-12 & IFNg	PMID: 12883732 PMID: PMC1782893
Increase Th2	Marijuana	Decreases IFNg	PMID: PMC4002943
Increase Treg			
Decrease pro-inflammatory	Ginger Curcumin Resveratrol	Decreases IL-6 Decreases IL-6 Decreases IL-1	PMID: PMC3712229 PMID: PMC4427355 PMID: PMC3488075

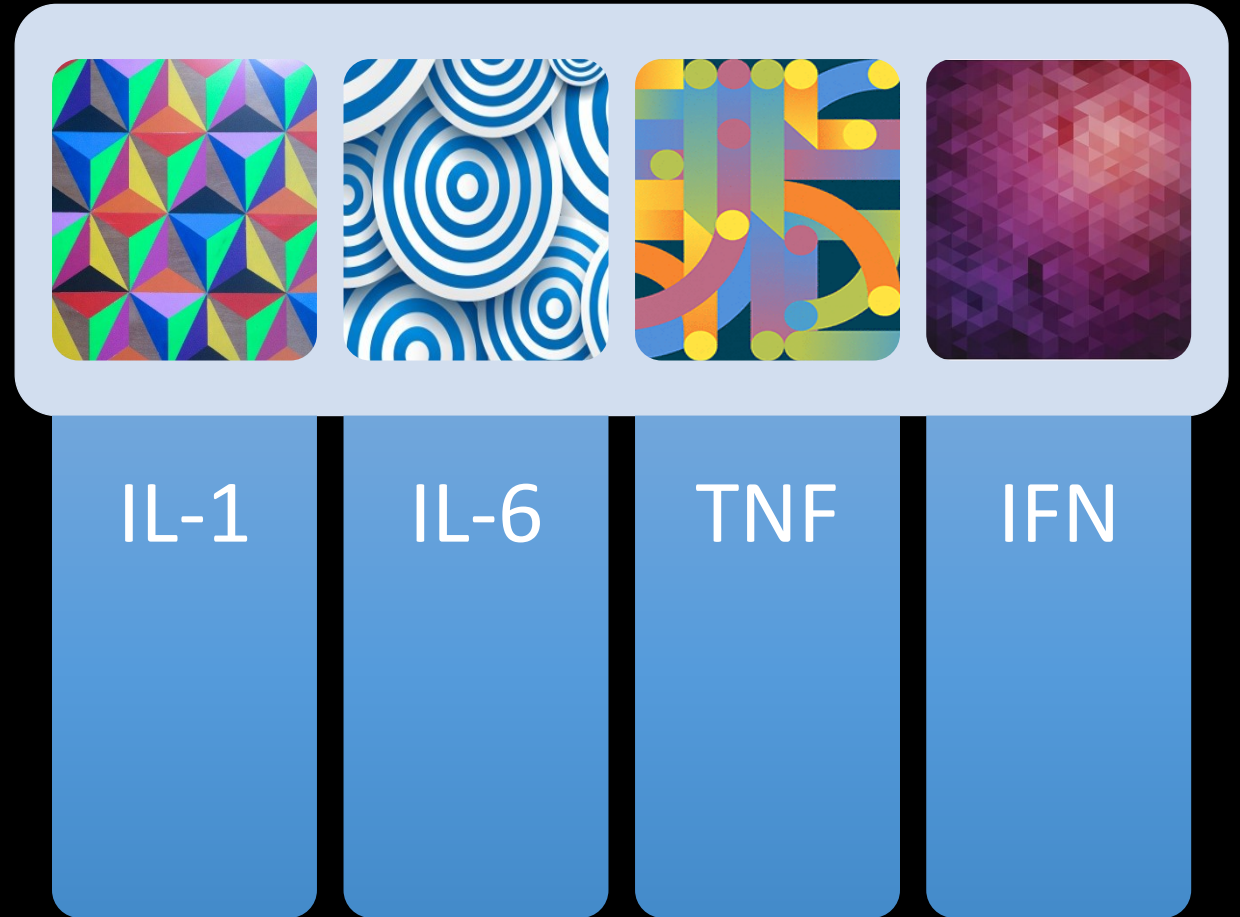
Immunological Relationship to Symptoms



- Borrelia antigen 'swims' through extracellular matrix
 - As antigen presentation expands, CD8s attack cells progressively further and further from the original antigen from the tick bite.

Immunological Relationship to Symptoms

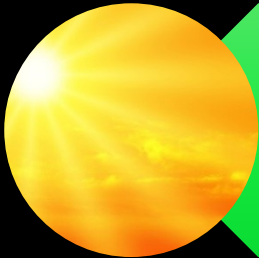
- Arthritis
- Fibromyalgia
- Fatigue
- Multiple Sclerosis
- Lupus



Decrease IL-1, IL-6, TNF, and IFNgamma



Bifidobacteria probiotics

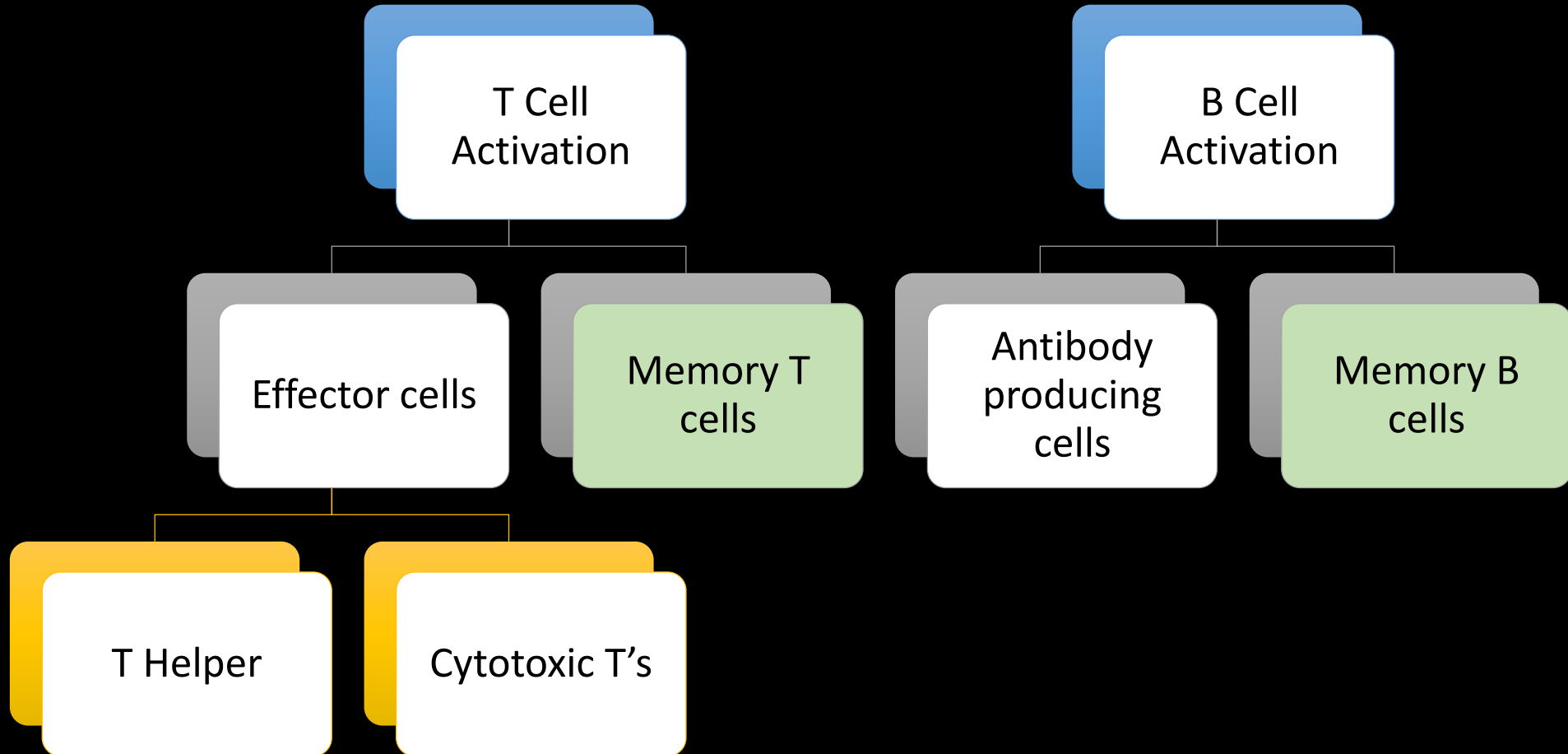


Vitamin D



Feverfew

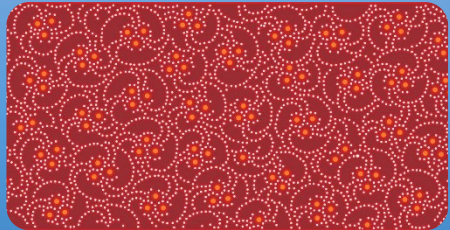
End of Response



Memory Cells



100-1000 fold more cells



Memory CD8's → No costimulation
(CD86)



Most memory reactions require CD4s

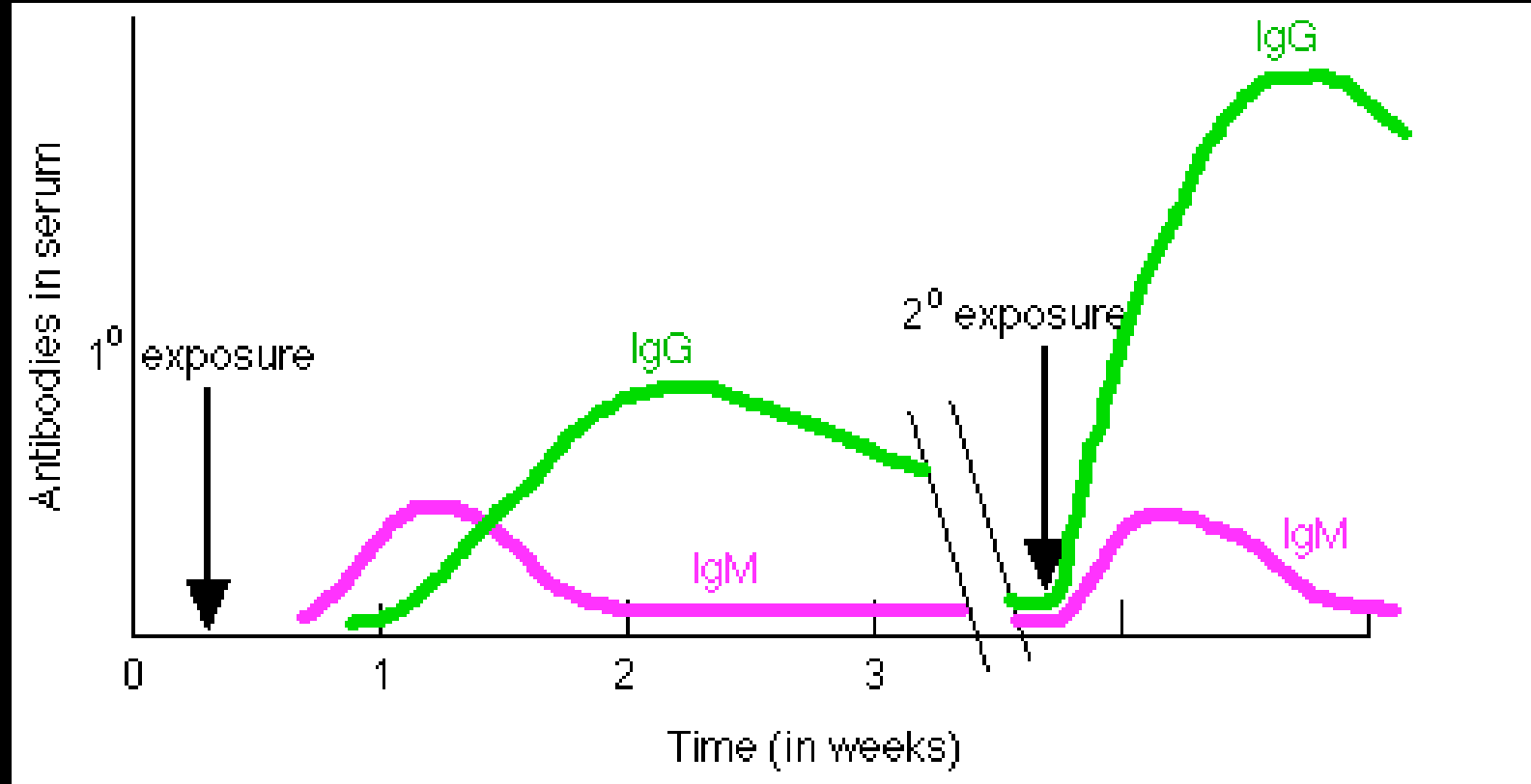
Characteristics of Memory

Memory responses are significantly shorter than the initial response

Initial response → 7 days

Memory response → 3-4 days

Memory can last as long as 23 years



Mini-quiz 2

1. Which cytokines and antibodies are involved in a Th1 response?
2. What is the ideal cytokine to increase to combat Lyme disease?
3. Which cytokines would you want to decrease during chronic Lyme?

Summary

1. Cytokines are responsible for many symptoms that people feel.
2. The ideal response to an infection is Th1 – IFNgamma and IgG
3. Infections can lead to autoimmune disease.
4. Cytokine types are in balance with each other.
5. Manipulating the cytokine response can improve health.

Thank you!

*'He who has health,
has hope;
and he who has hope,
has everything.'*

- Arabian proverb



NUTRITION



PARKINSON'S



MEMORY



TRAVEL



HEALTH

NATURAL MEDICINE
MEETS SCIENCE

with Heather Zwickey



Eating Better for Parkinson's – on Amazon!

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EATING BETTER
FOR PARKINSON'S

About This Site

Hi there! I research, teach, travel, lecture and write about nutrition. And in

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National Center for
Complementary and
Integrative Health