

NATIONAL HUMAN GENOME RESEARCH INSTITUTE



Metabolism, Infection and Immunity in Mitochondrial Disease

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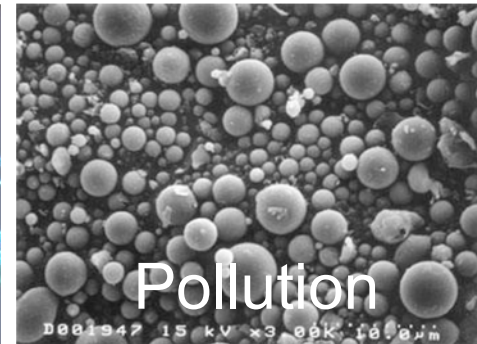
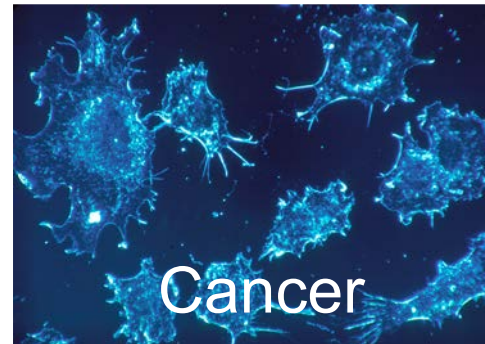
No conflicts of interest to declare

Outline

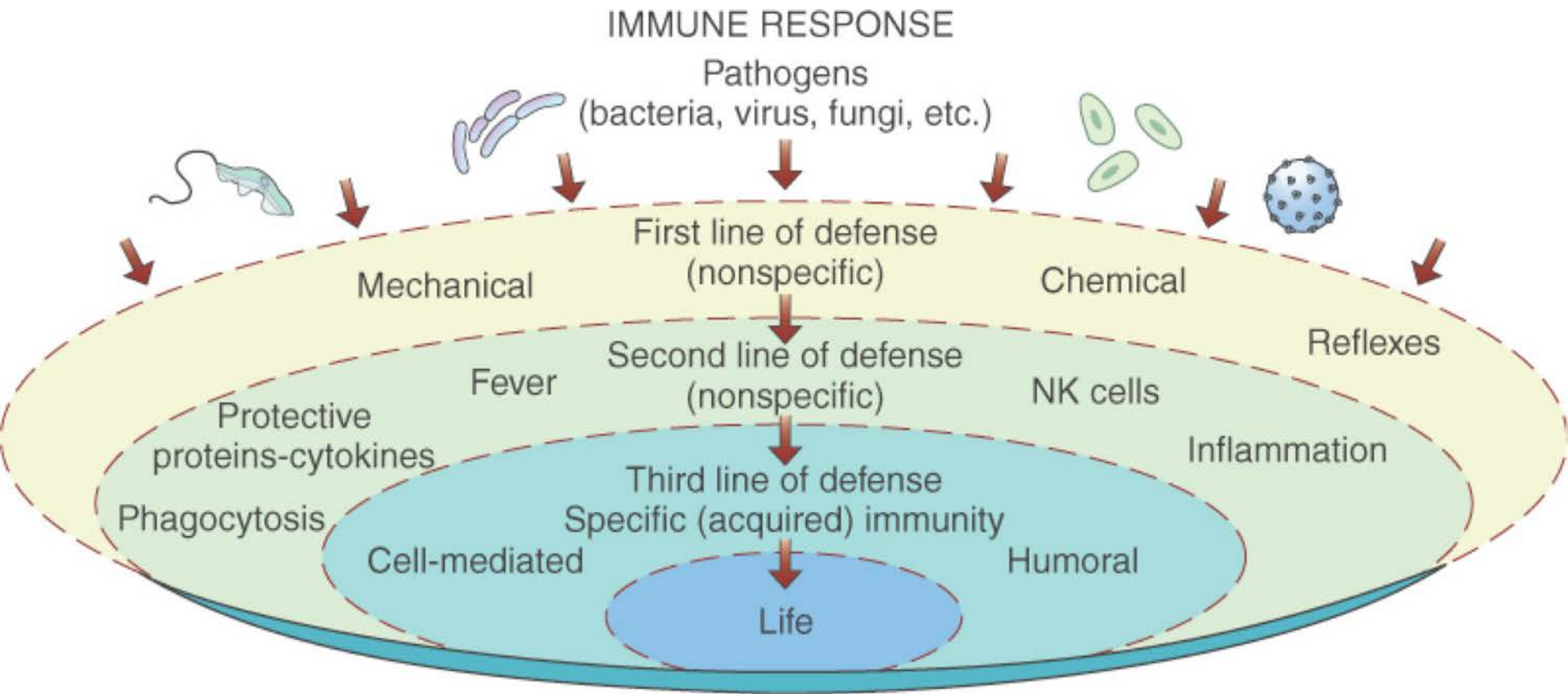
- What is the immune system and why is it important?
- Infection and mitochondrial disease
- Immune function in mitochondrial disease

Why is the immune system important?

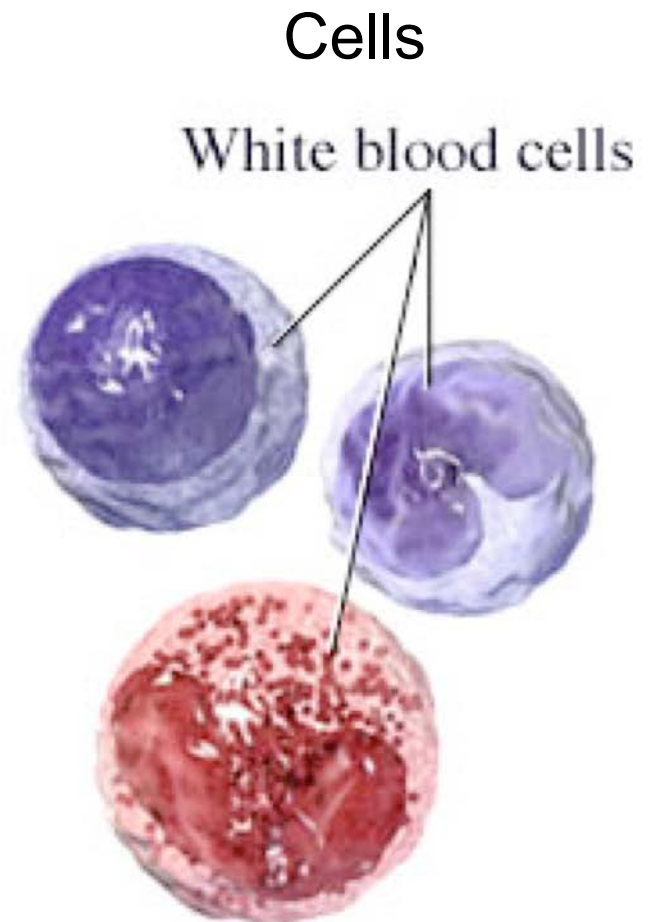
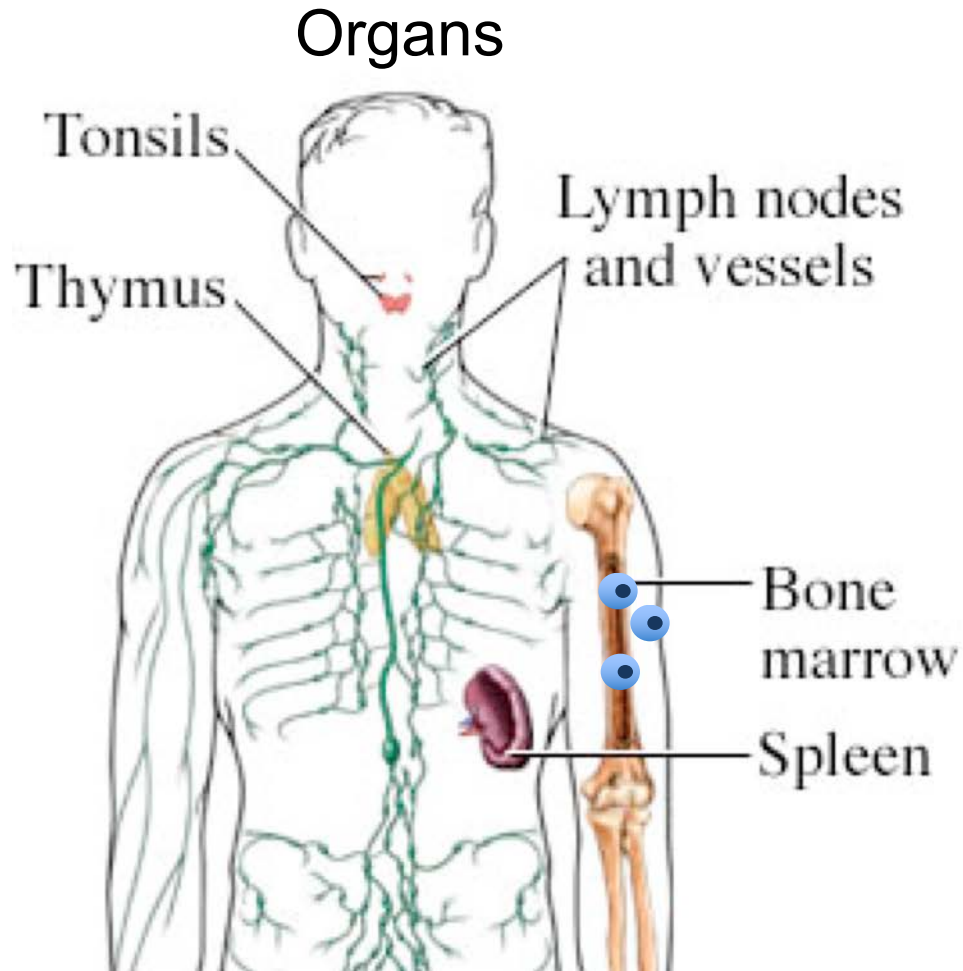
- Protects us against



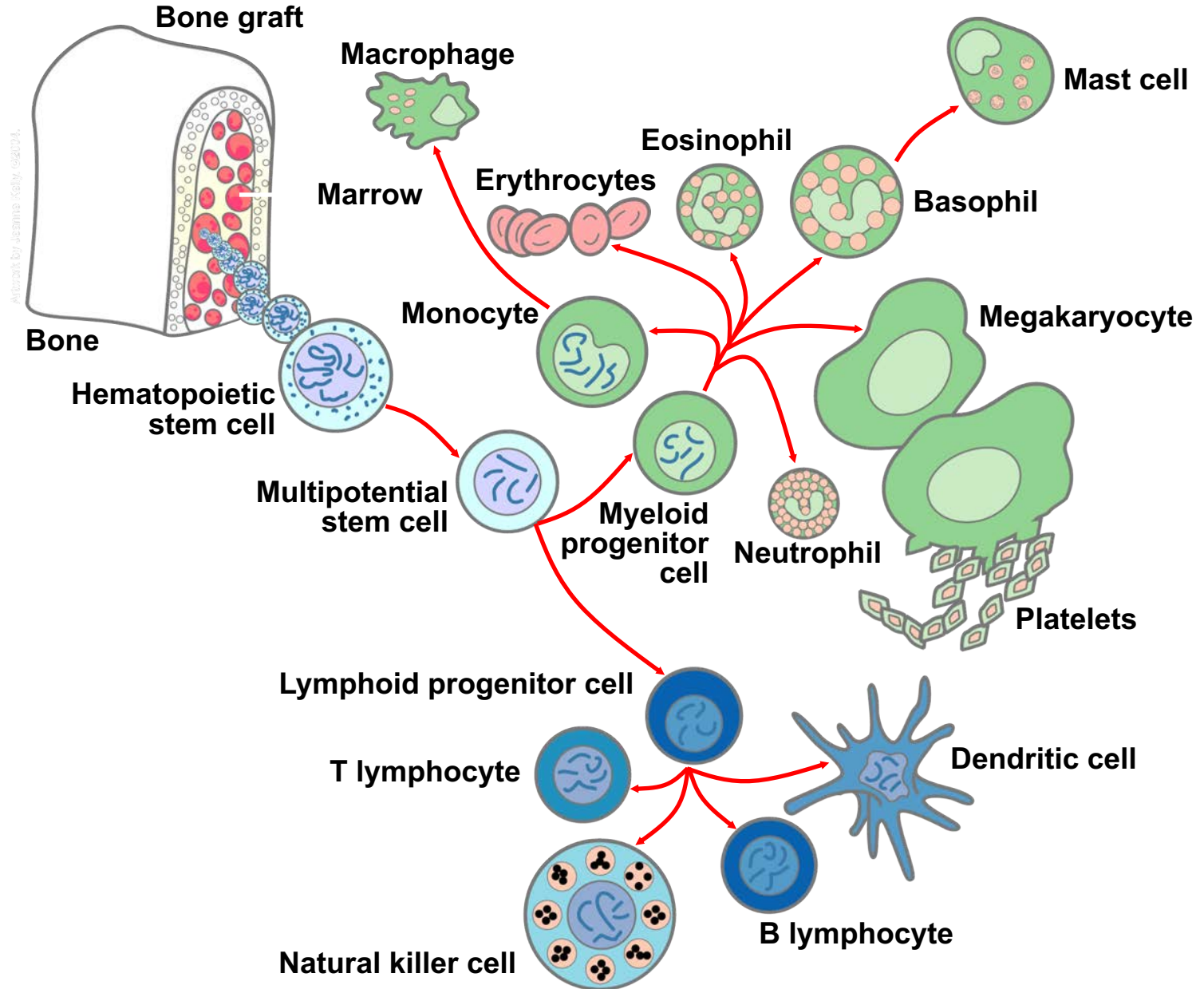
The immune system has multiple lines of defense



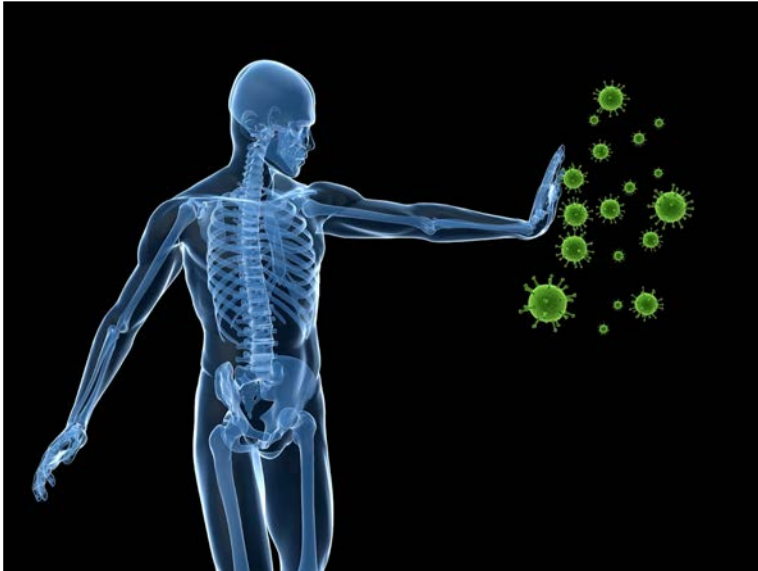
The immune system is composed of organs and cells



The immune system has many different type of cells

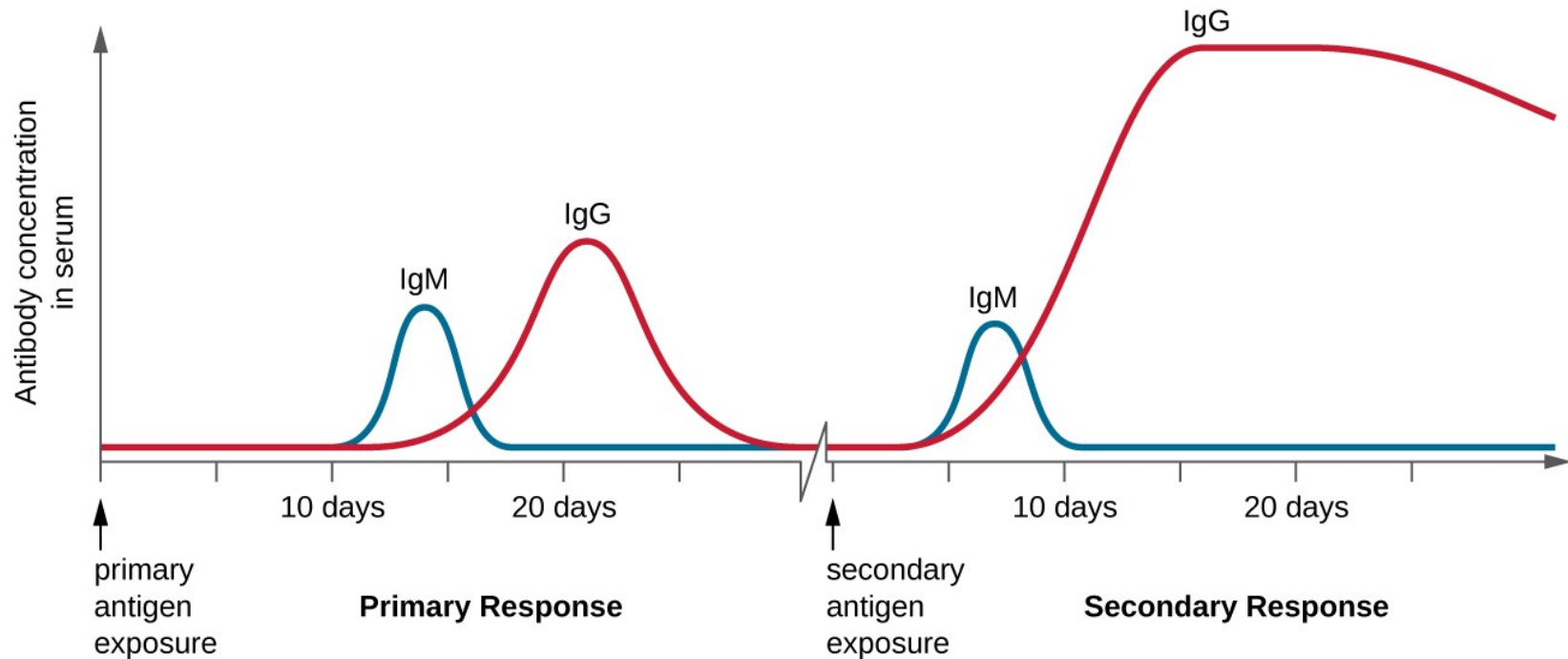


How does the immune system protect us?

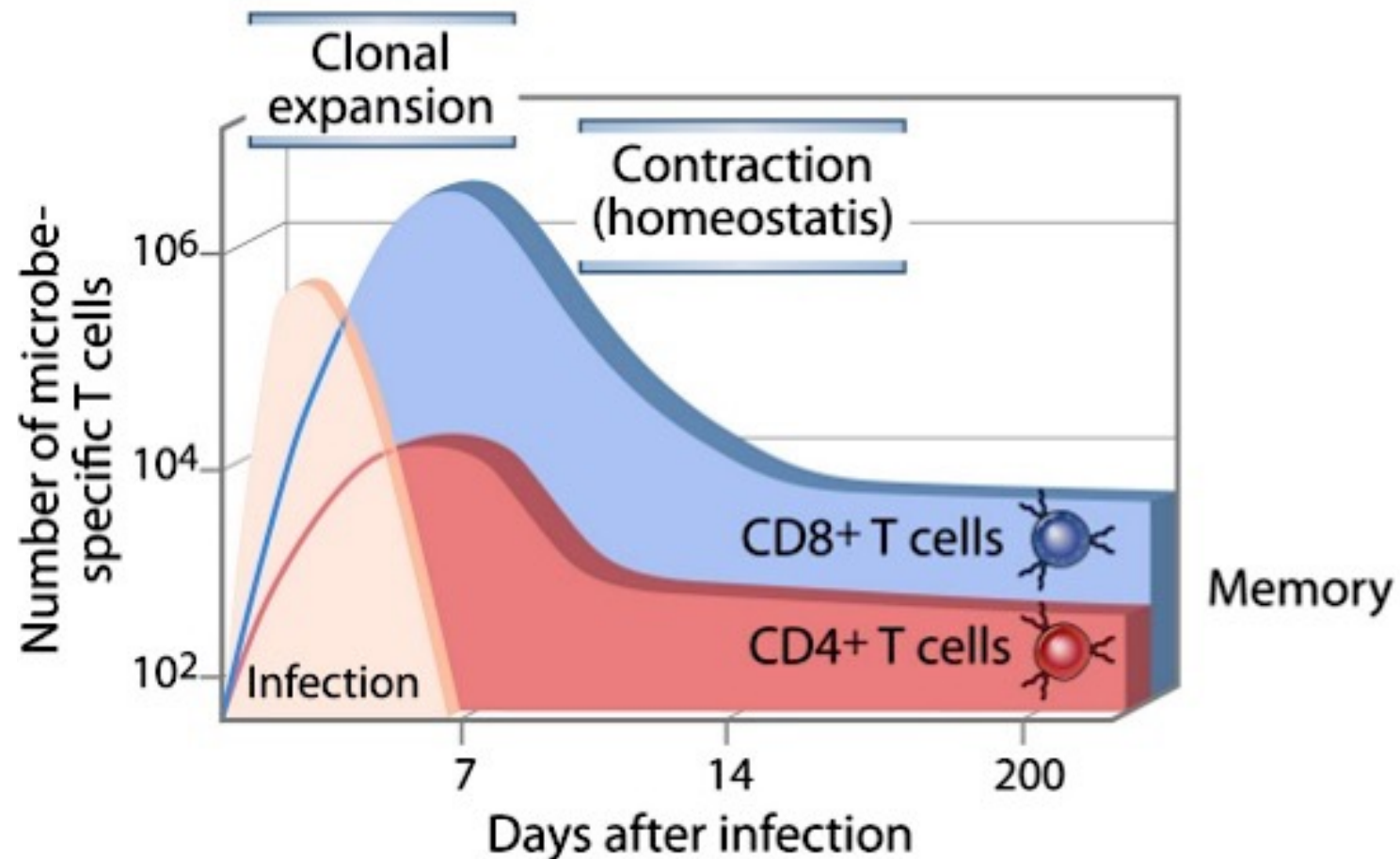


- Body learns to defend itself by:
 - Natural infection
 - Vaccination

How does the immune system protect us?



How does the immune system protect us?



Why study the immune system immune and mitochondrial disease (MD)?

- Because:
 - Infection is bad for patients with mitochondrial disease
- Our questions:
 - What happens to patients with MD during infection?
 - Does having MD affect immune function?



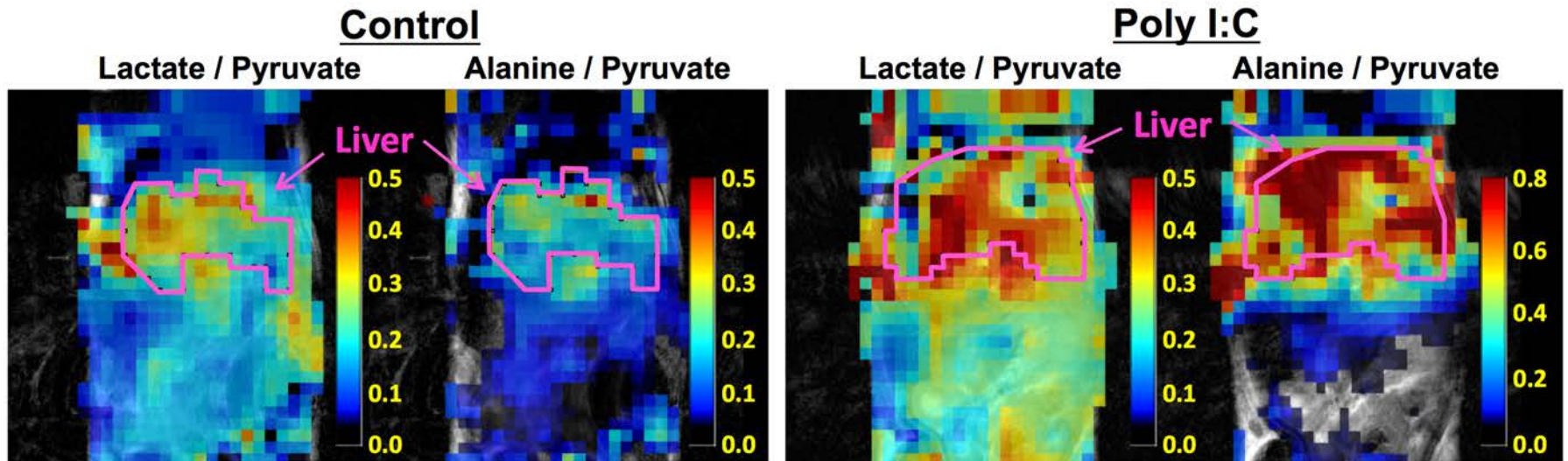
Infection is bad for patients with MD

- **Point #1:** Infection increases energy requirements
 - For every 1° C of fever, metabolic rate can increase 10% or more
 - **Problem:** need more calories, but you don't feel like eating; ↓ ability to generate energy



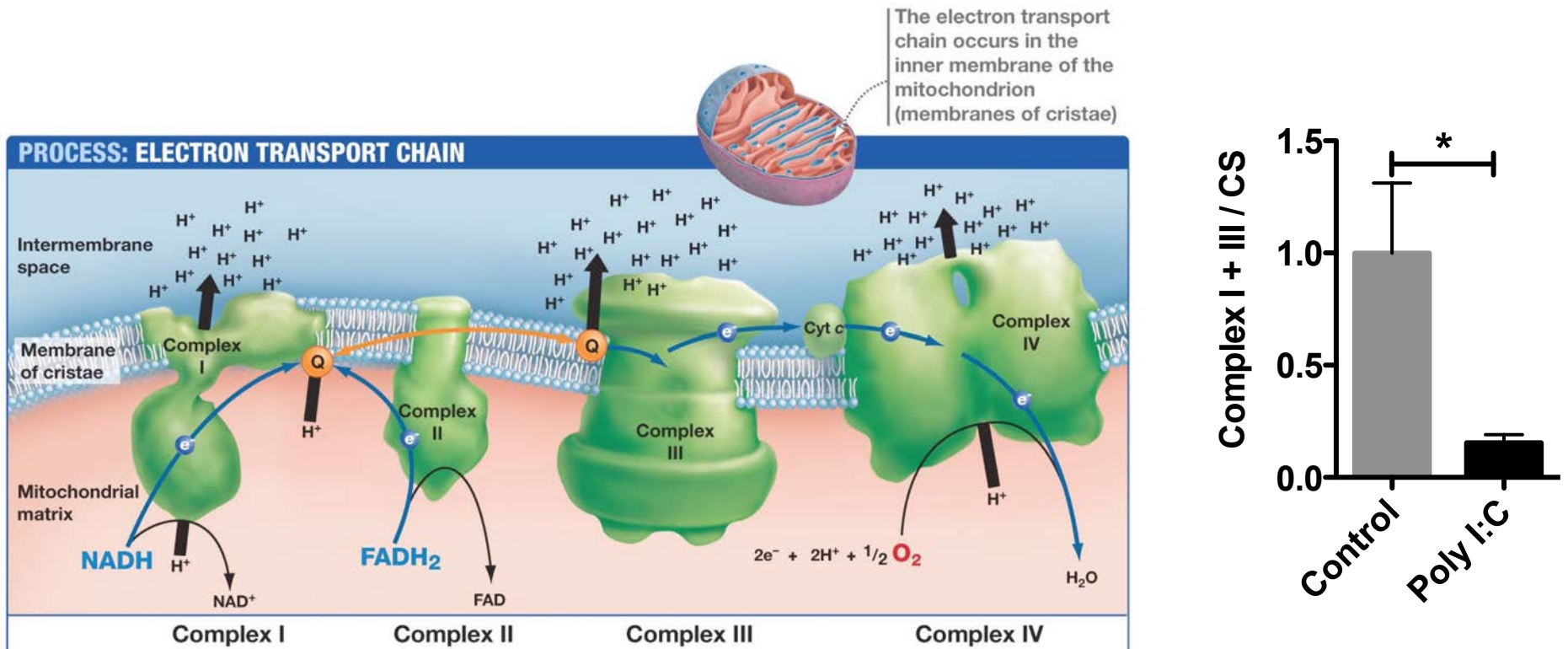
Infection is bad for patients with MD

- **Point #2:** Infection can lead to an increase in tissue lactate production



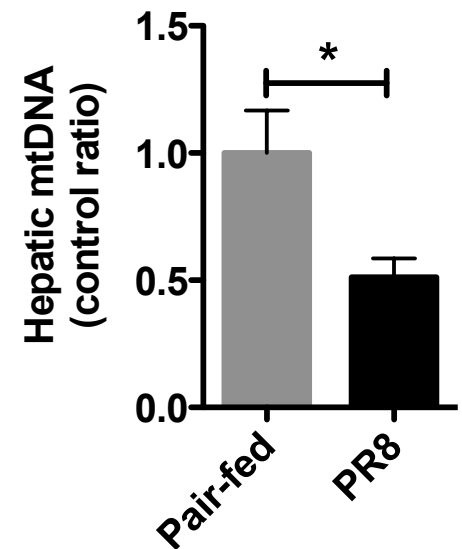
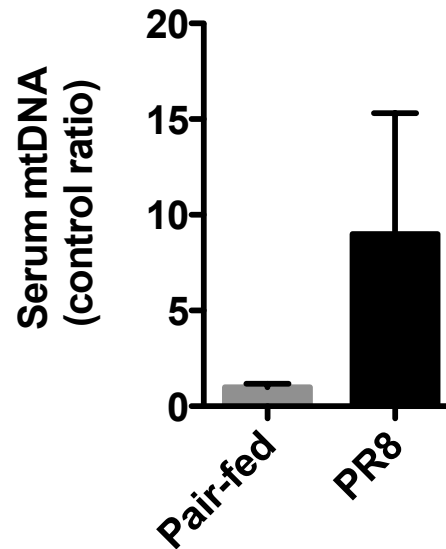
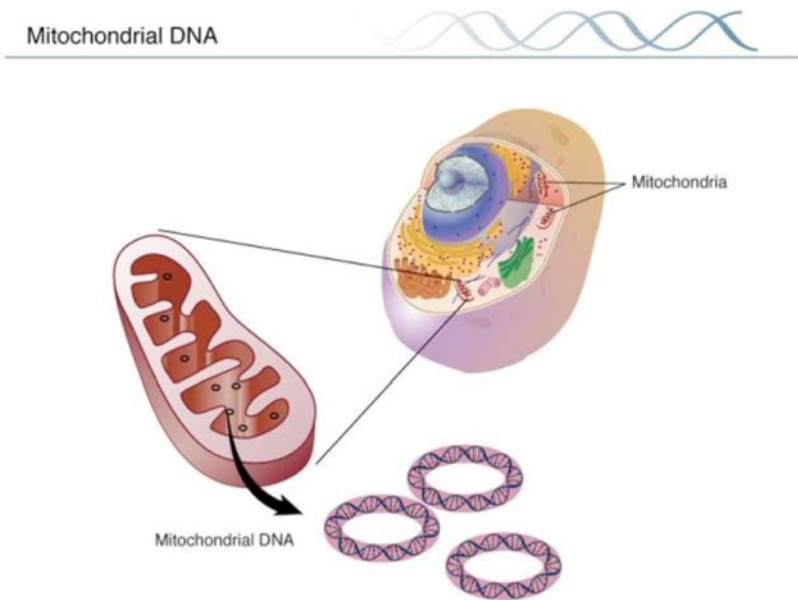
Infection is bad for patients with MD

- **Point #3:** Immune reactions can damage mitochondria



Infection is bad for patients with MD

- **Point #3:** Immune reactions can damage mitochondria



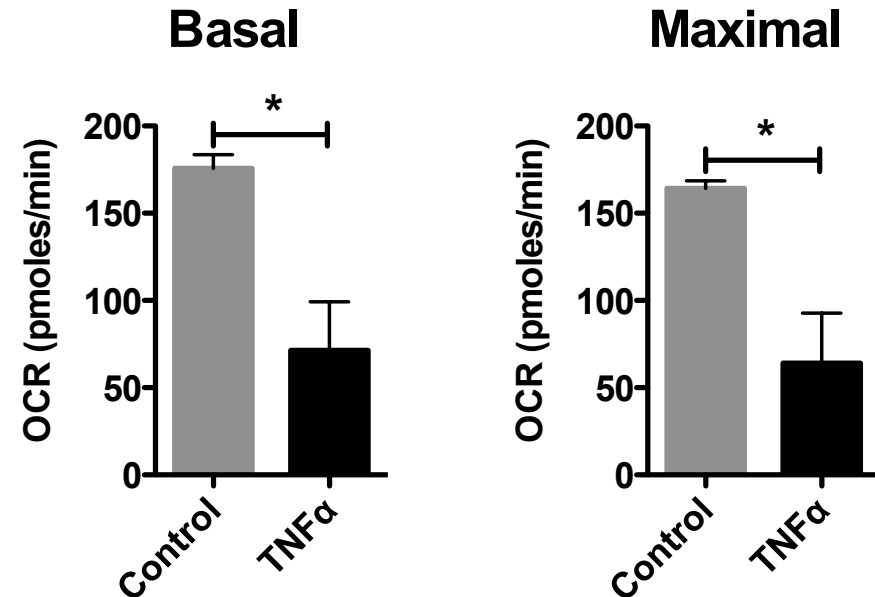
Infection is bad for patients with MD

- **Point #4:** The immune response may be part of the problem - cytokines



Immune cells “text”
each other by cytokines

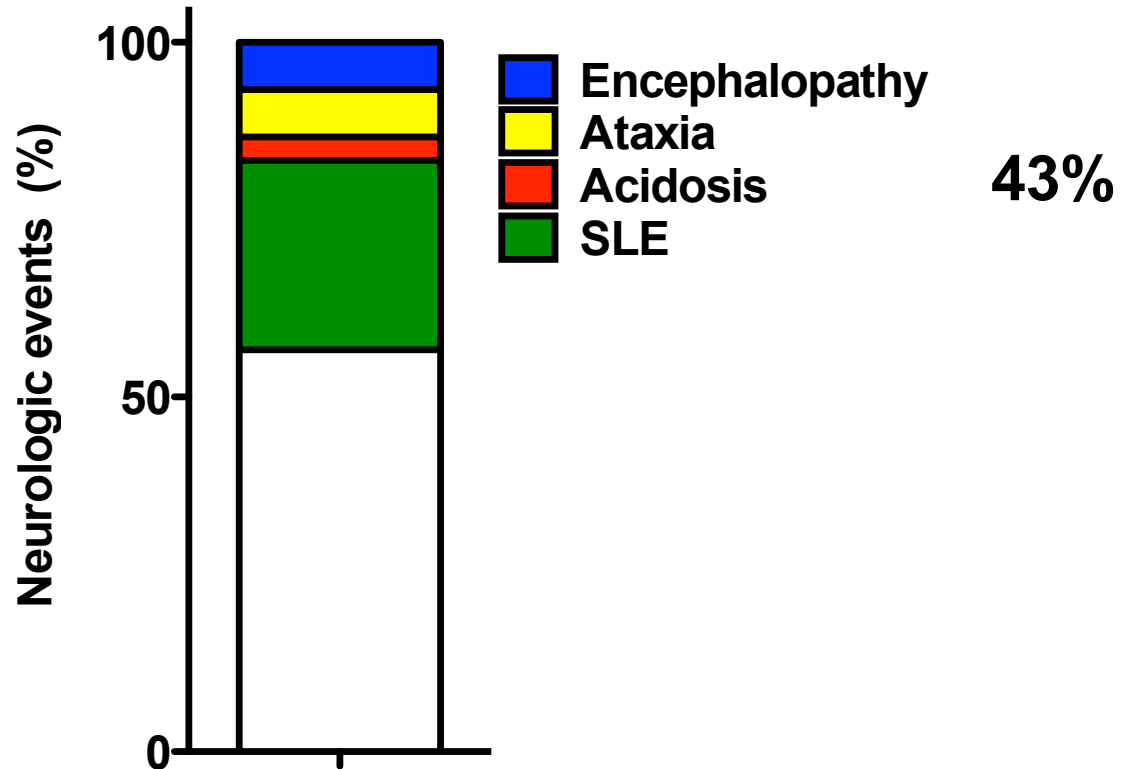
May be innocent
bystanders (e.g. liver)



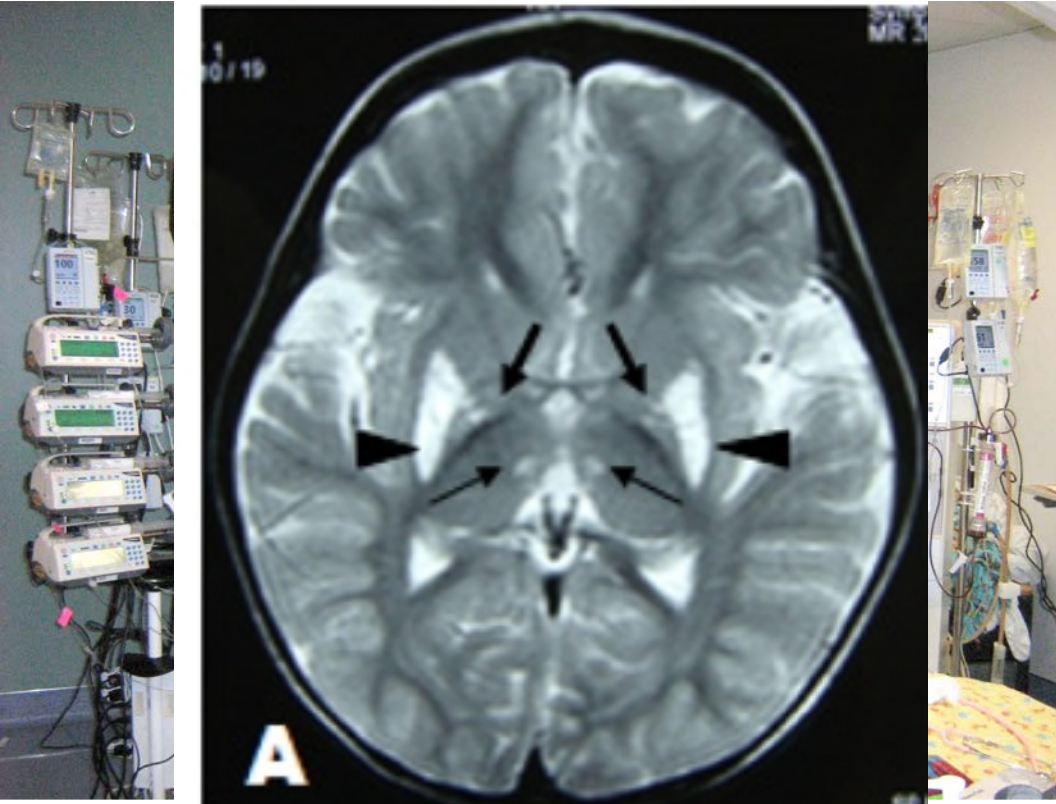
Cytokines produced as part of the immune response inhibit mitochondrial metabolism in human liver cells.

Infection is bad for patients with MD

- **Point #5:** What do we see clinically with infection?



The need for translational research in MD



Metabolic decompensation

- *In extremis* (life-threatening)
 - Bioenergetic failure
 - Lactic acidosis
 - Organ failure (e.g. liver failure)
 - Encephalopathy
 - Stroke
 - Sequelae
- Extensive ICU care

Clinical question: How did we arrive at this point?

1) Are patients with MD immunodeficient?

2) What is the role of inflammation in MD pathophysiology?

Immune function in MD

- Since infection can be very serious...
 - How well does the immune system function in patients with MD?



Fatal Neonatal-Onset Mitochondrial Respiratory Chain Disease with T Cell Immunodeficiency

JANINE REICHENBACH, RALF SCHUBERT, RITA HORVÀTH, JENS PETERSEN, NANCY FÜTTERER, ELISABETH MALLE,
ANDREAS STUMPF, BORIS R. GEBHARDT, ULRIKE KOEHL, BURKHART SCHRAVEN, AND STEFAN ZIELEN

- mtDNA depletion syndrome
- ↓Complex II+III and IV in muscle
- Recurrent infections, RIP 18 months with septicemia
- Hypogammaglobulinemia by 15 months
- ↓Memory T-cells, CD8+ T-cells, NK cells
- ↓T-cell response to IL-2

Clinical Communications

Predisposition to infection and SIRS in mitochondrial disorders: 8 years' experience in an academic center

Melissa A. Walker, MD, PhD^a, Nancy Slate, MS^b,

Alexandra Alejos, BS^c, Stefano Volpi, MD^d,

Rajashri S. Iyengar, MD, MPH^c, David Sweetser, MD, PhD^e,

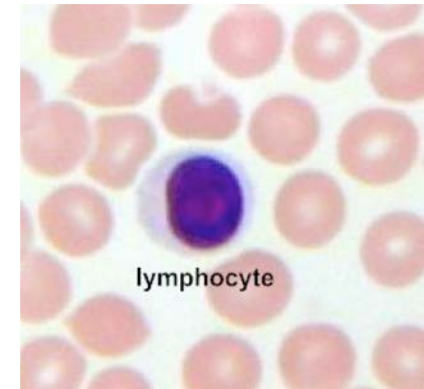
Katherine B. Sims, MD^{a,*}, and Jolan E. Walter, MD, PhD^{c,*}

Clinical Implications

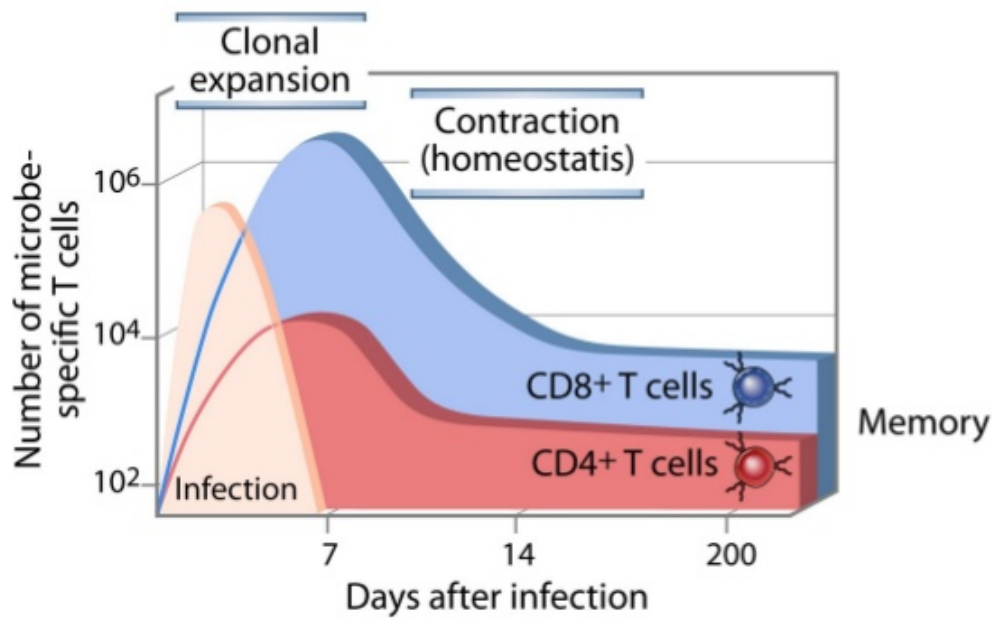
- Mitochondrial disorders are multisystem diseases that, although not previously described, may include predisposition to infection and immunodysfunction.
- Immune phenotyping of these patients may be useful to identify individuals who require immunoglobulin replacement and/or antibiotic prophylaxis to decrease hospitalization and improve outcomes.

Immune function and MD

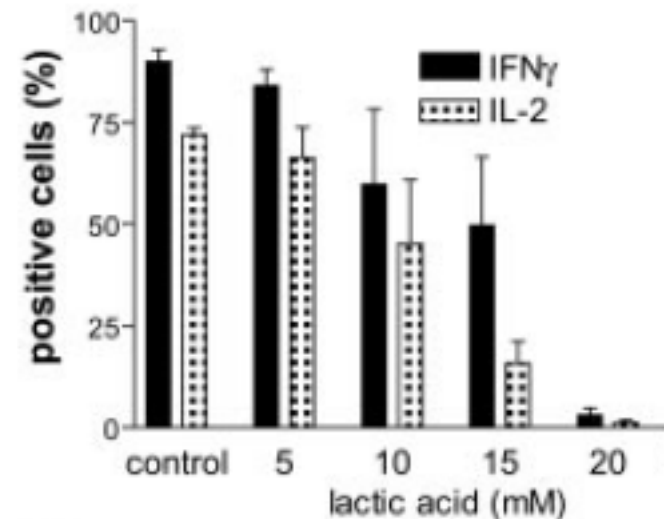
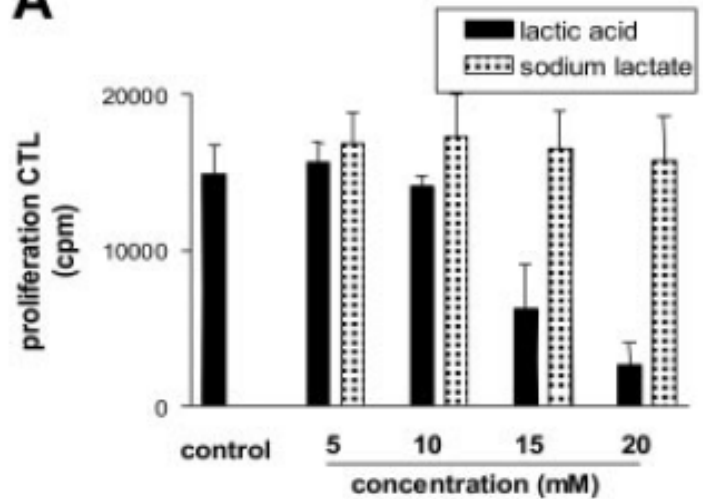
- What do we know? Not much, but...
 - Immune cells don't like high levels of toxins
 - Mitochondrial RC deficiencies can also be present in immune organs and cells



Immune function and MD: toxins (lactate)



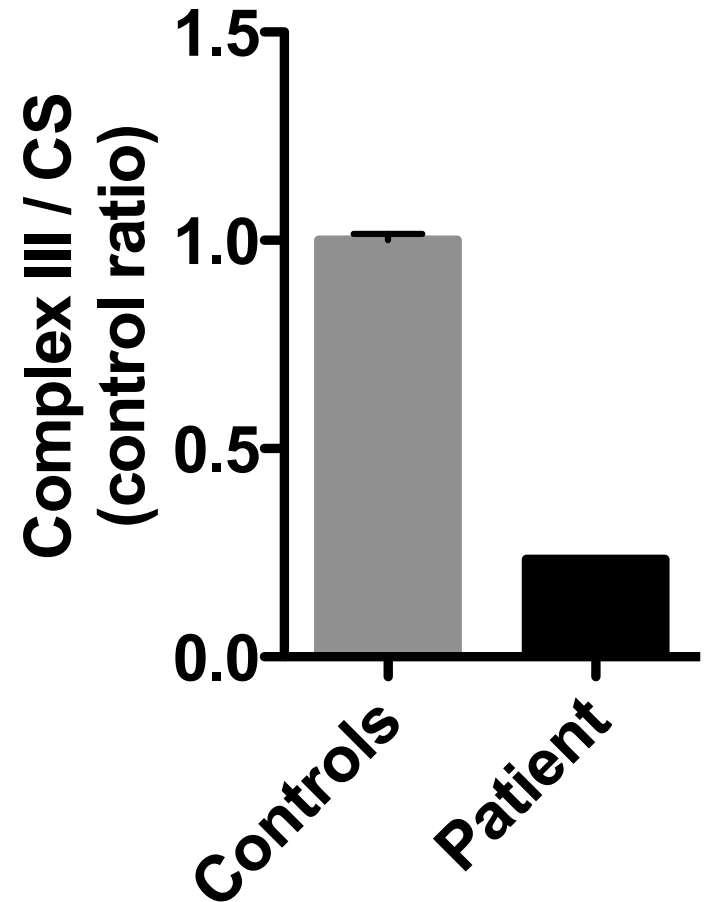
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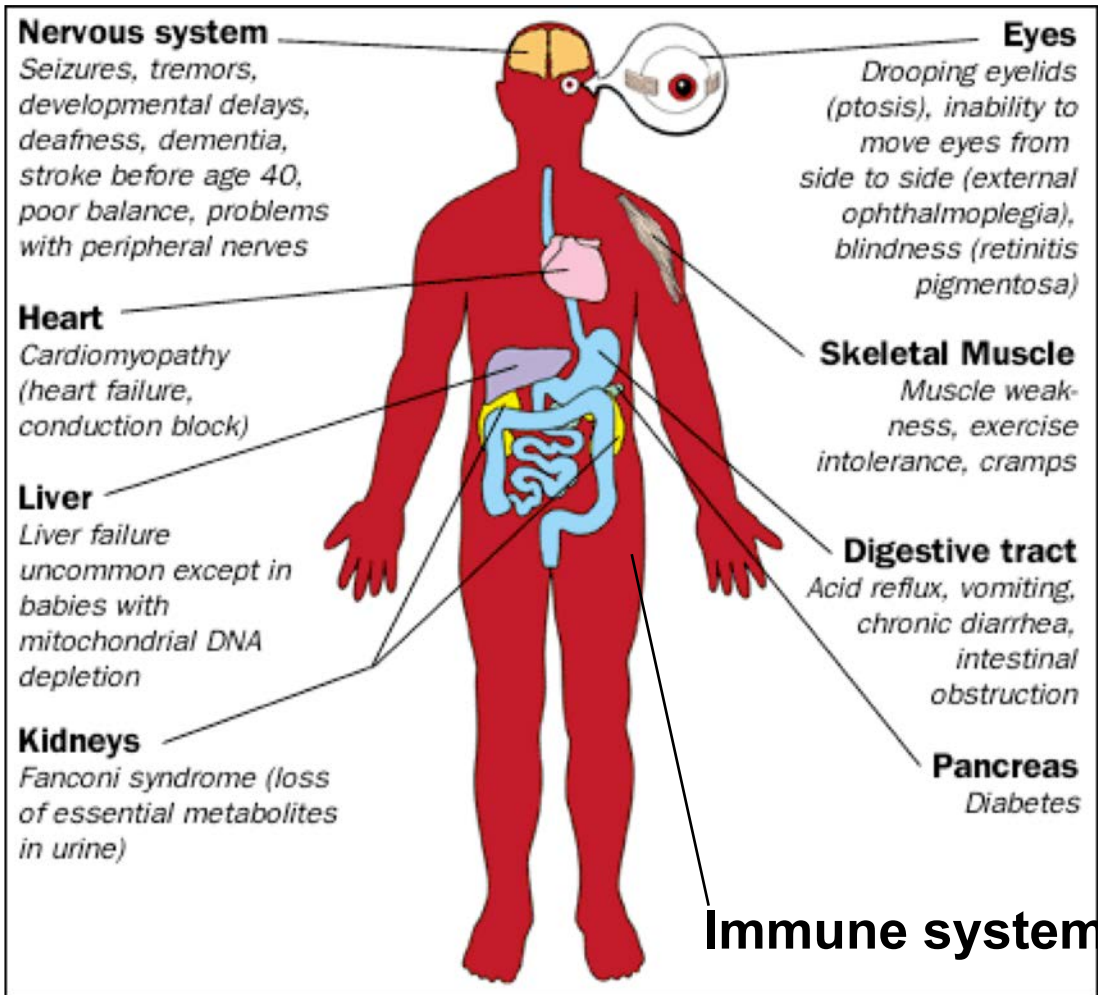
Mitochondrial dysfunction in immune cells

It all started with a clinical case...

- 15 year old male
- Complex III deficiency
- Multisystem disease
 - Neurologic
 - Musculoskeletal
 - Endocrine
 - Immunologic
 - Multiple infections
 - Hypogammaglobulinemia
 - Loss of pneumococcal titers
- Research exome pending

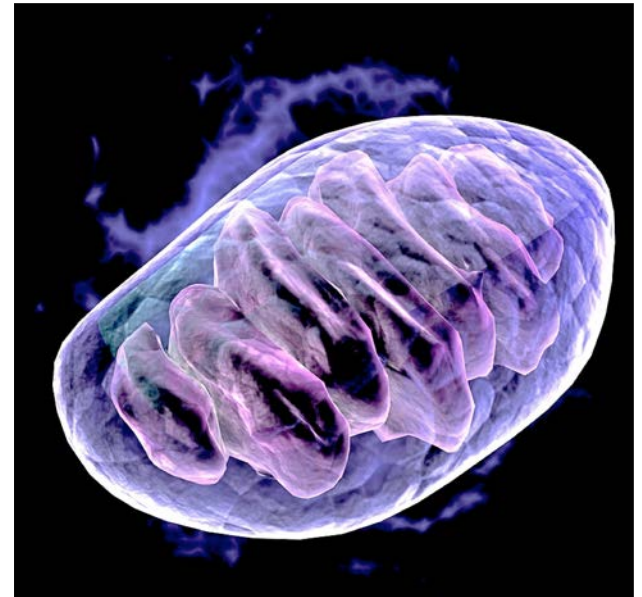
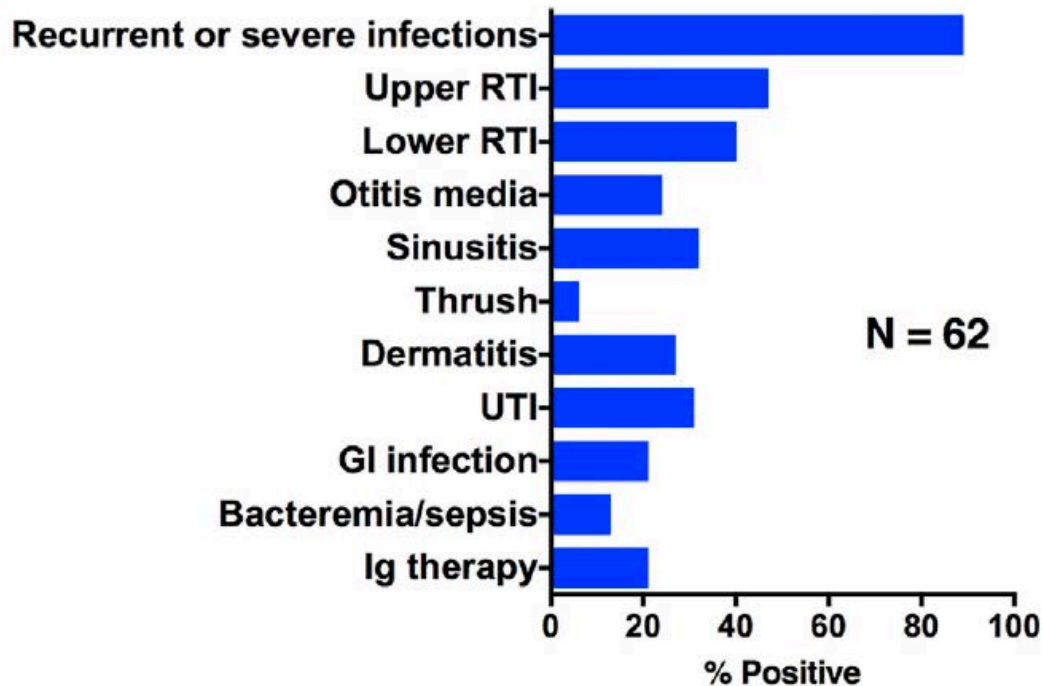


Clinical features of MD

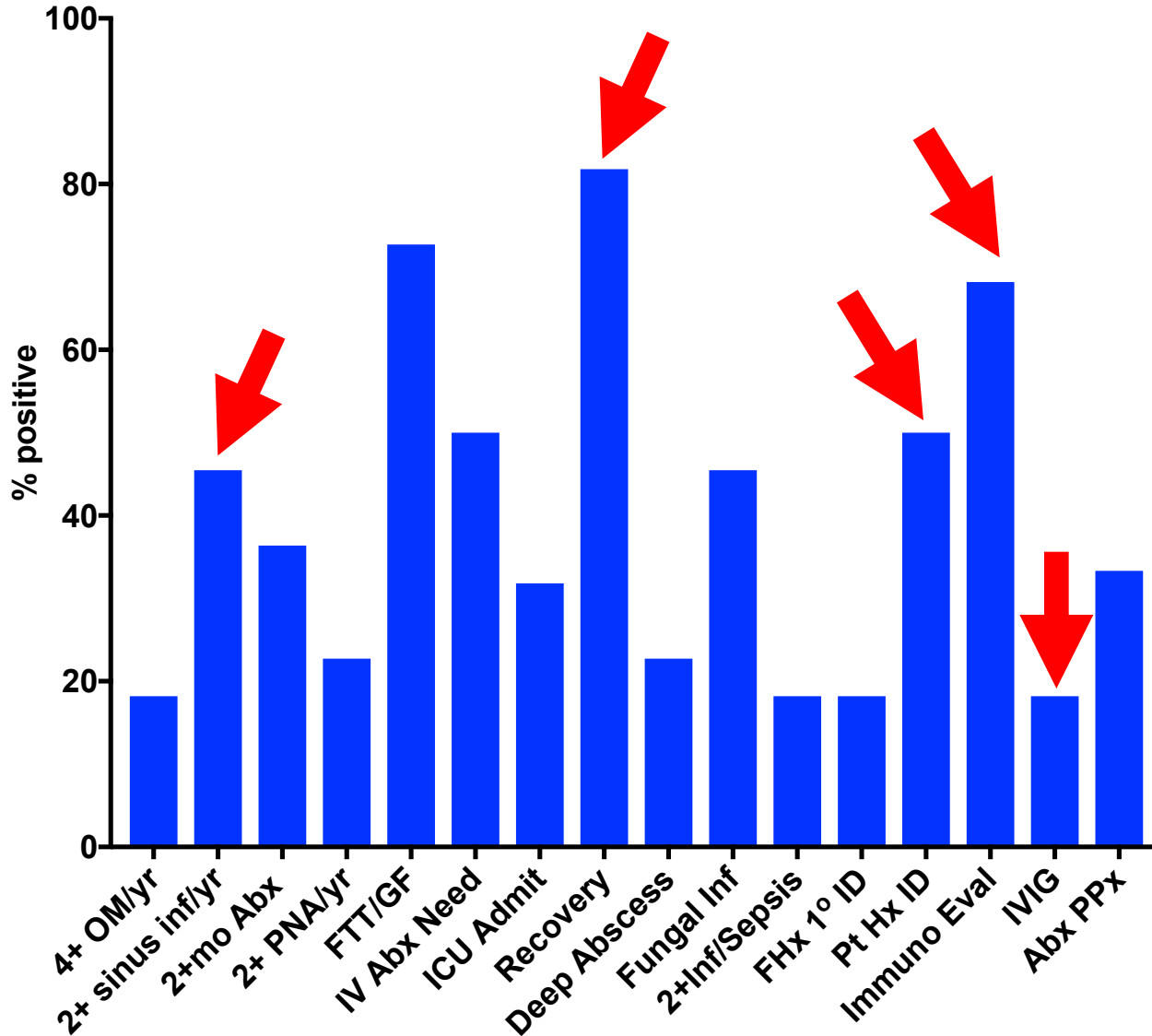


- Multisystem
- ↑energy organs
- mtDNA and nDNA inheritance
- Most common IEM
- Lactic acidosis
- **Complications during/after decompensation**
(Edmonds et al, 2002)
- **Pathophysiology:** energy deficiency, ROS

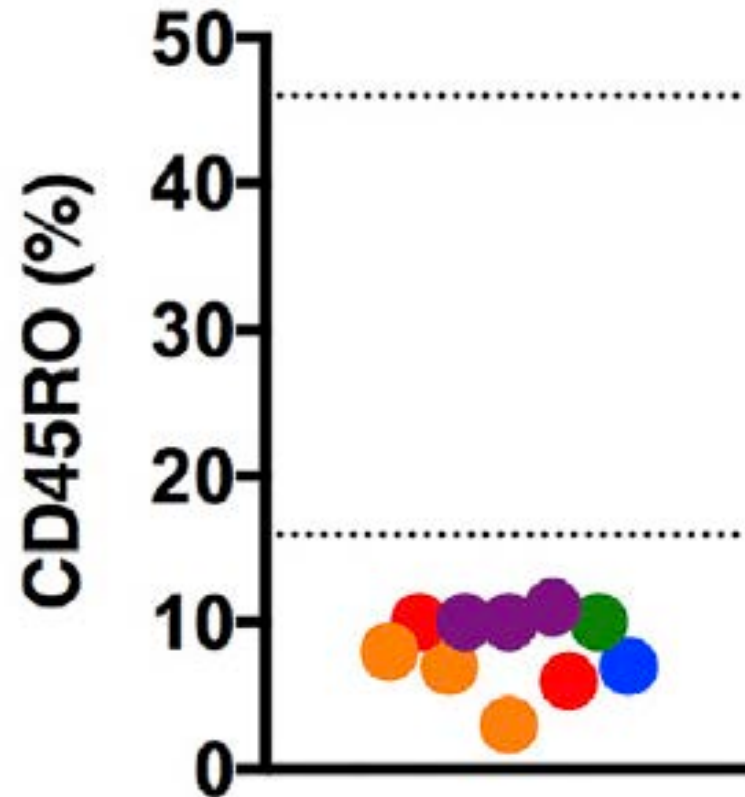
Recurrent infection is common in patients with MD



Immunodeficiency screen for MD patients



Patients with MD may have poor immune memory



Immunization Recommendations for Children With Metabolic Disorders: More Data Would Help

Michael T. Brady, MD

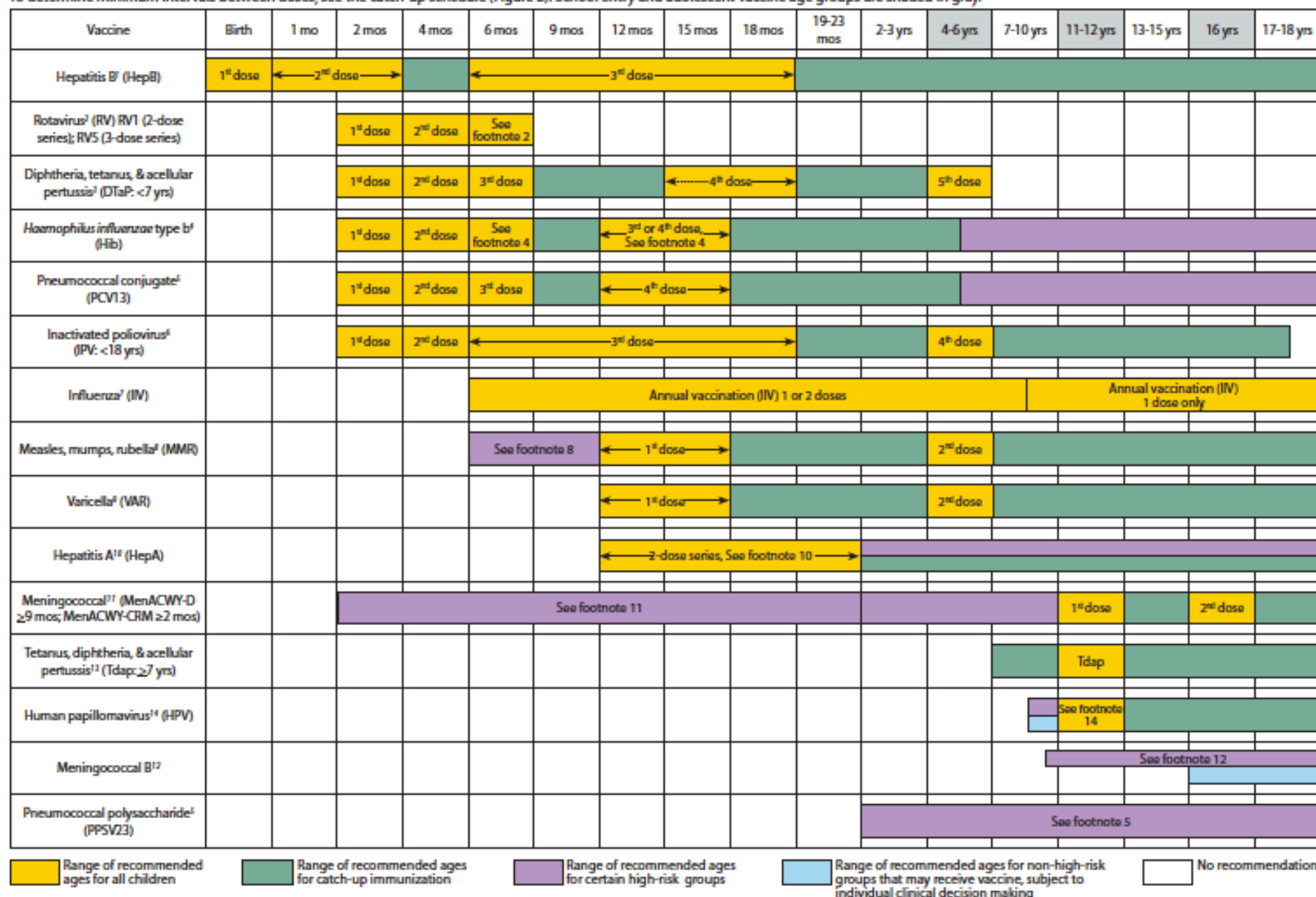
Department of Pediatrics, Columbus Children's Hospital, Columbus, Ohio

Biochemical changes that are present in children with inborn errors of metabolism may affect their immune response system and not only increase risk for infection but also diminish their ability to develop protective immunity after immunization. Understanding the immunogenicity and ability of vaccines to provide protective immunity in each of the specific metabolic disorders will be critical to understanding the child's risk/benefit equation. Immunogenicity of vaccines and protection have not been well characterized in children with most metabolic disorders. A recent review⁵ of immune deficien-

Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2018.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).

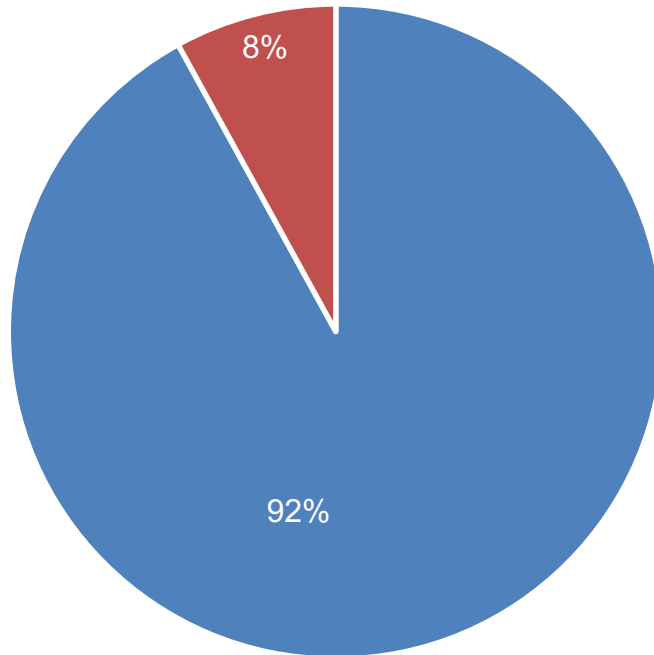
These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.



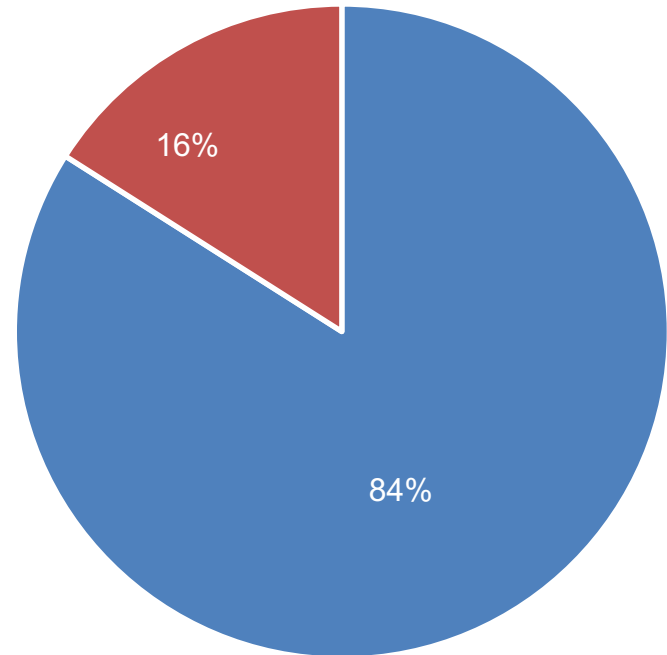
NOTE: The above recommendations must be read along with the footnotes of this schedule.

Vaccination Rate

Vaccination rates MMR

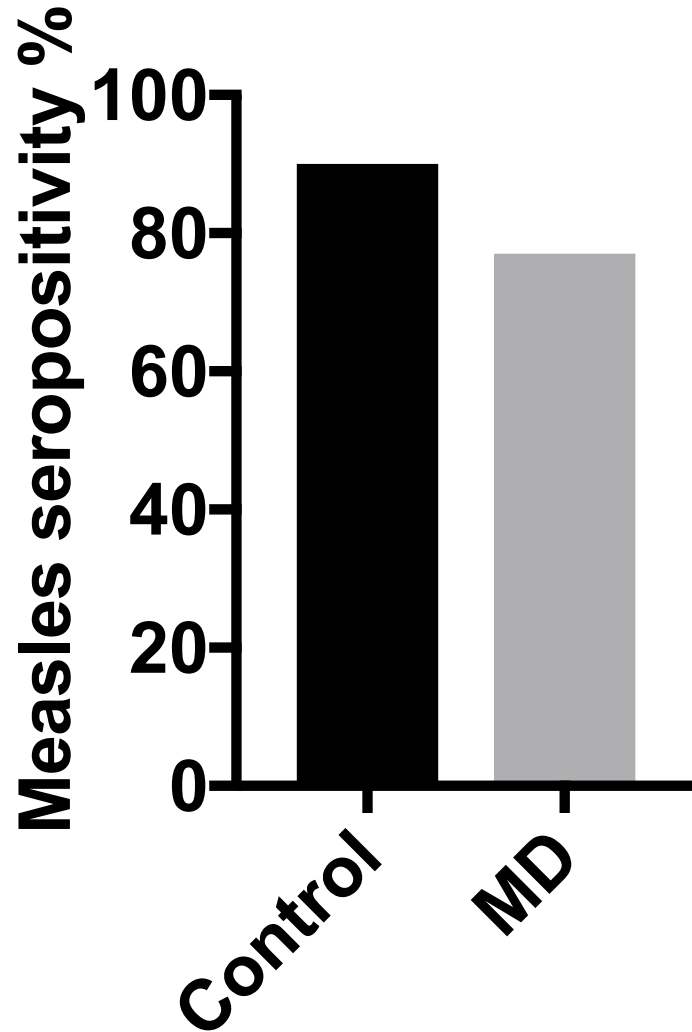


Vaccination rates VAR



YES
INCOMPLETE

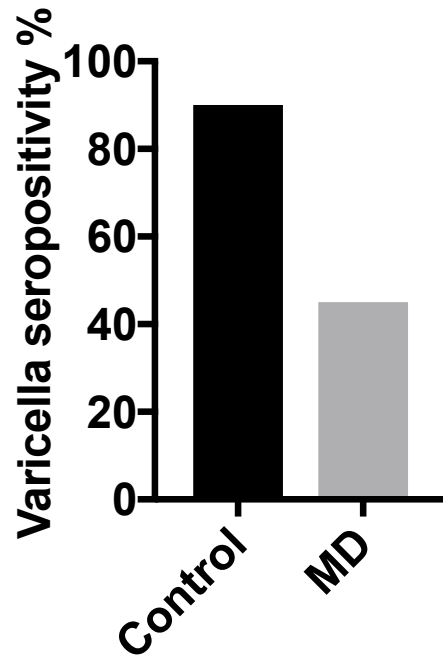
MMR seropositivity



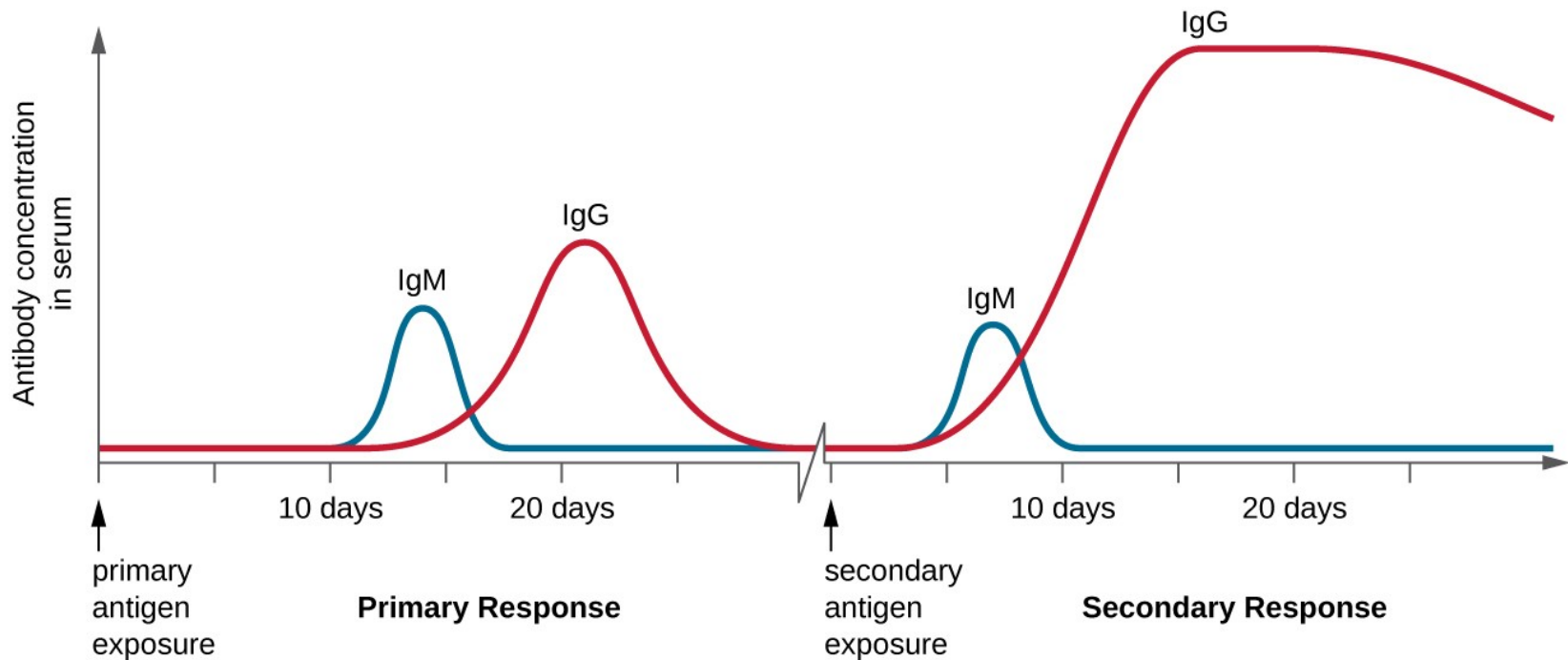
Measles cases per year

<u>Year</u>	<u>Cases</u>
2010	63
2011	220
2012	55
2013	187
2014	667
2015	188
2016	86
2017	118
2018	63

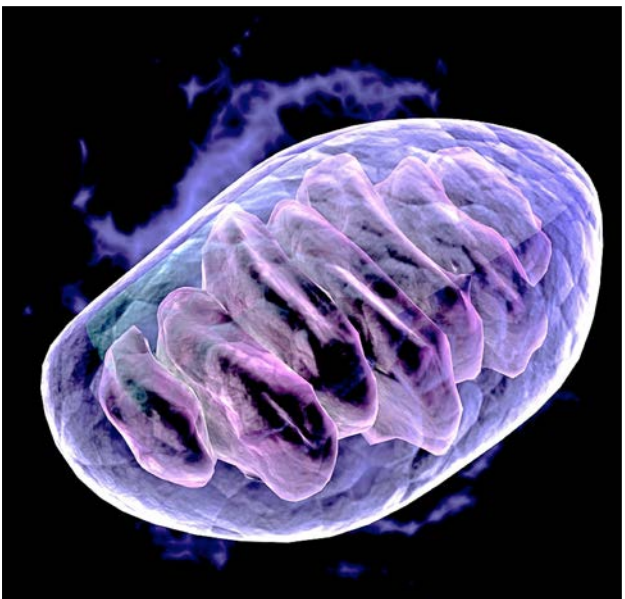
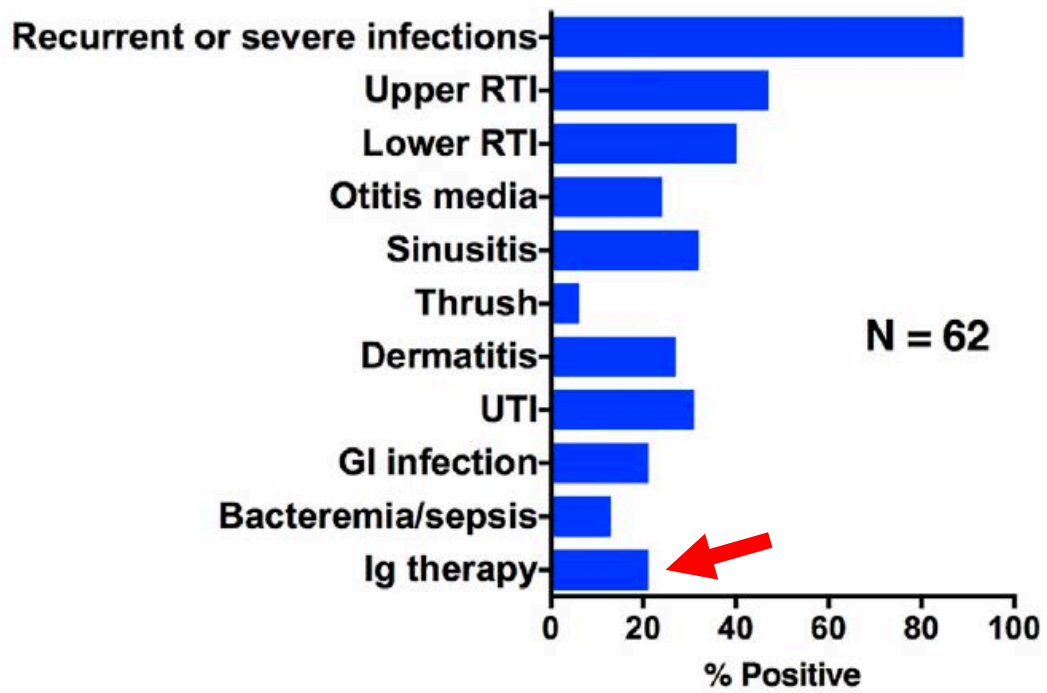
Varicella seropositivity



How does the immune system protect us?



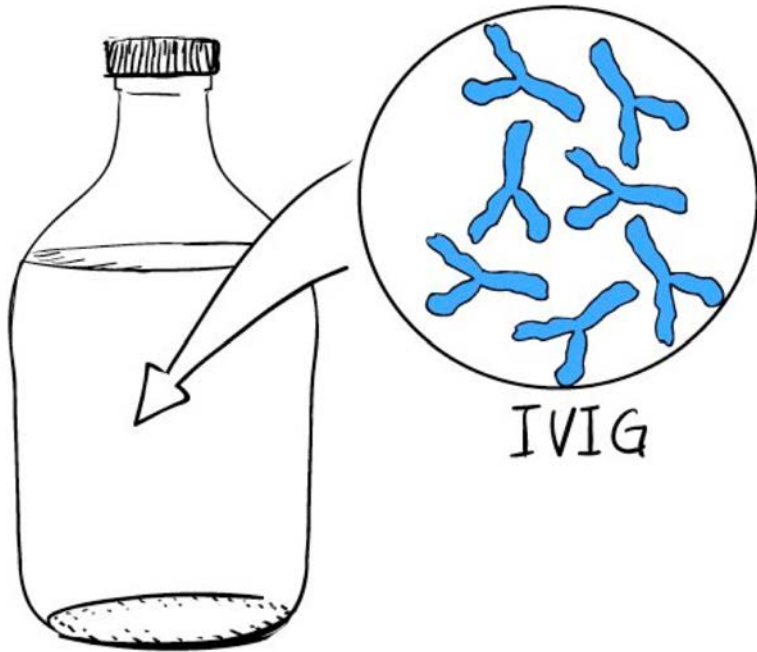
Hypothesis: Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.



**How many patients have
problems with infection?**

How many patients are on IVIg?

The mystery of IVIg

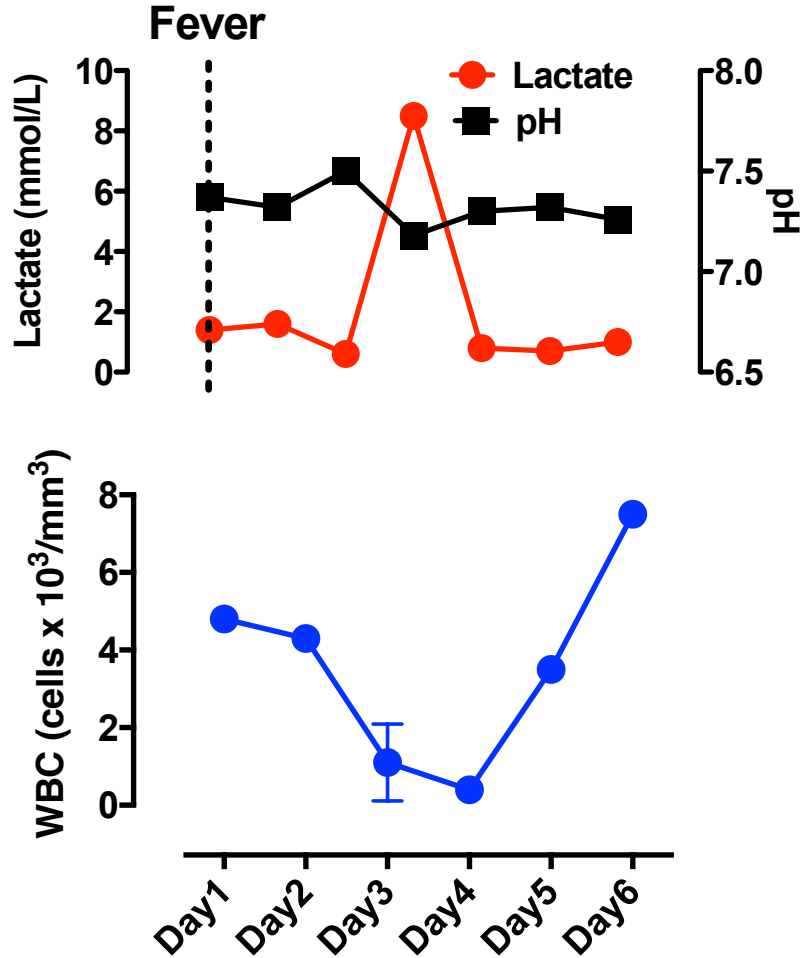


IVIg

- intravenous immune globulin
- aka “antibodies”
- produced from human plasma
- Immune mediated conditions
- Immunodeficiency
- Other effects? Benefits?
- Does the pathology of MD have an immune component?

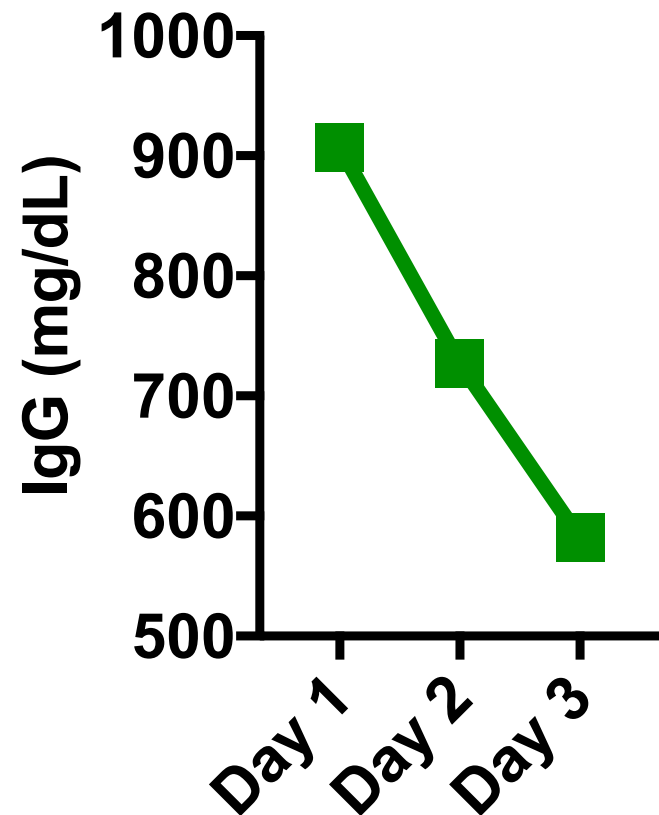
Hypothesis: Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.

- 8 y/o male with MD
- Received PICC line 2 weeks prior for access
- Presented with fever and hospitalized



Hypothesis: Bioenergetic deficiency in MD may extend to immune cells leading to immunodeficiency.

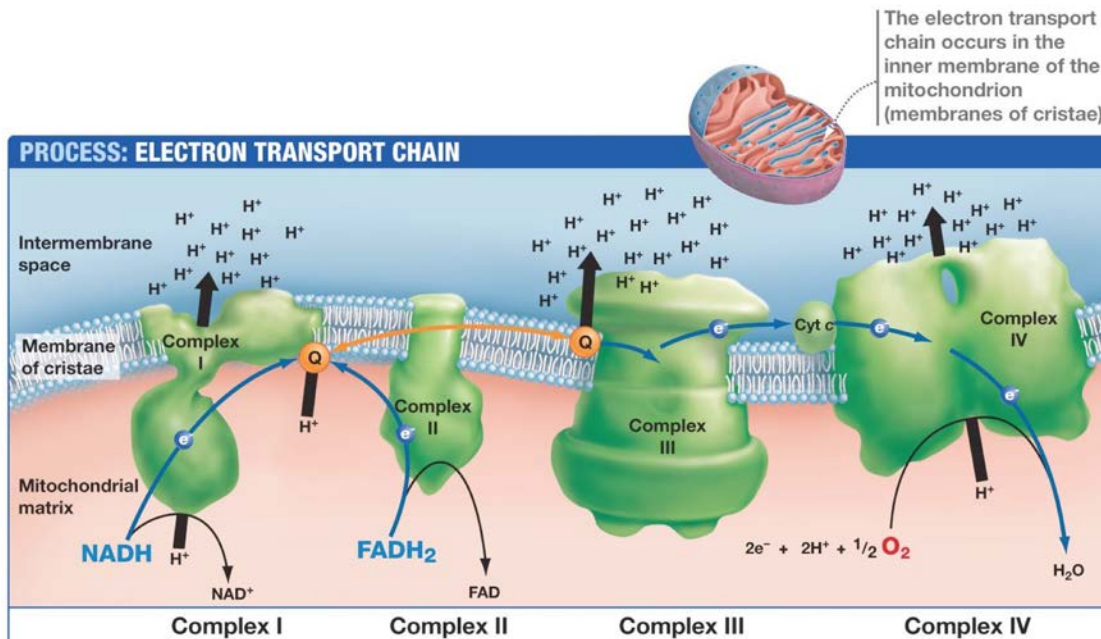
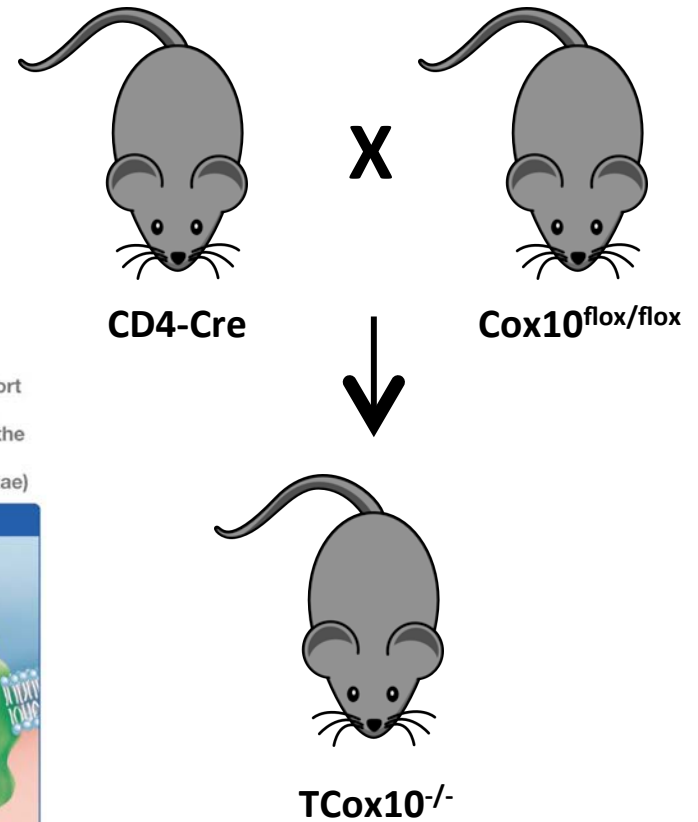
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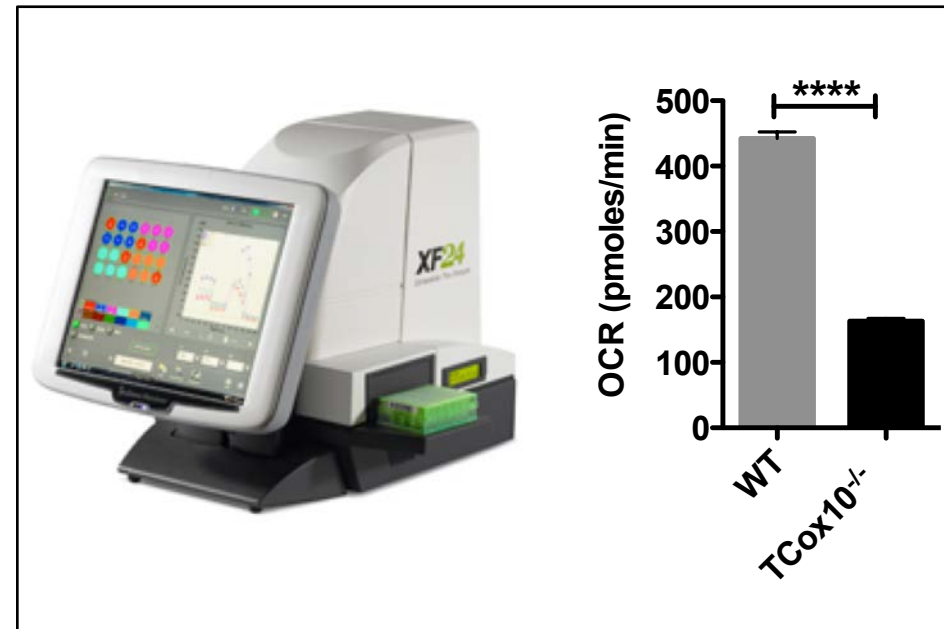
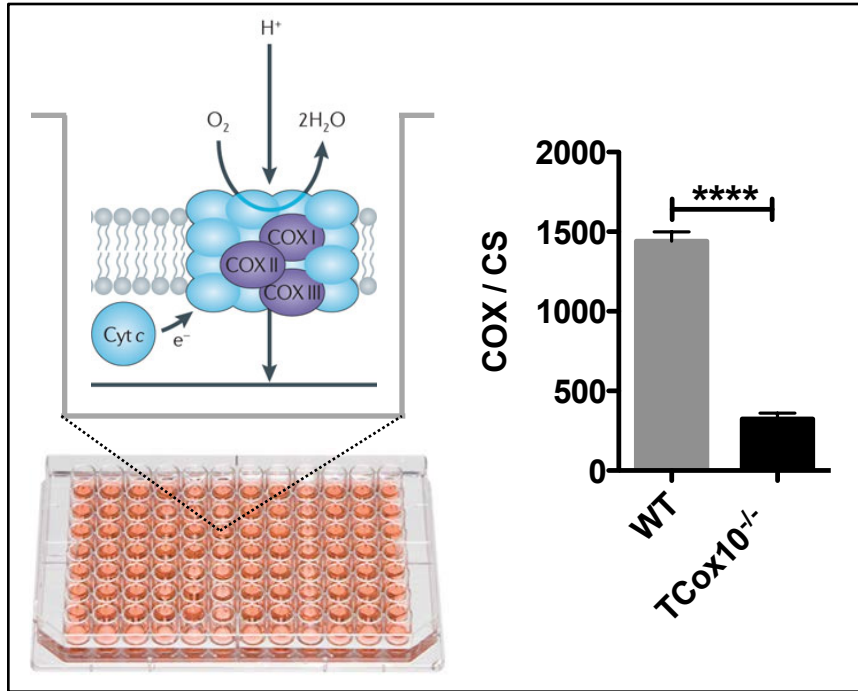
Translational model: TCox10^{-/-}

COX10

- Maturation of cytochrome C oxidase (CIV)
- Present in lymphocytes
- Deficiency: MD or Leigh phenotype
- KO in T-cells only
- Mice are generally healthy

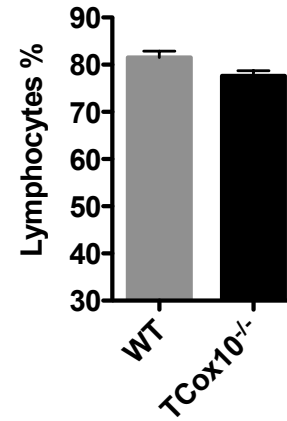
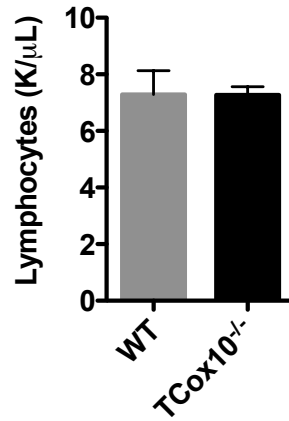
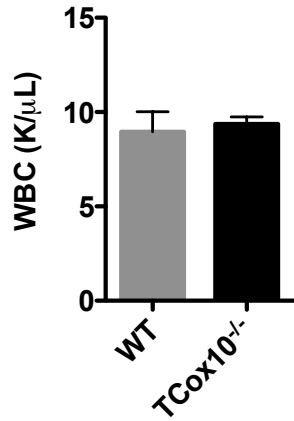


Compromised respiratory chain in TCox10^{-/-} T-cells



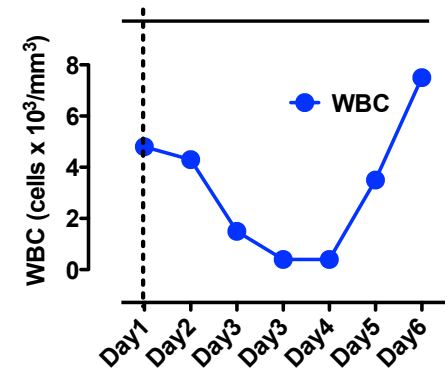
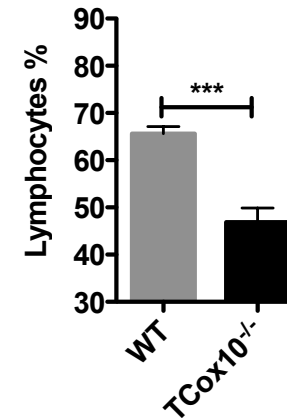
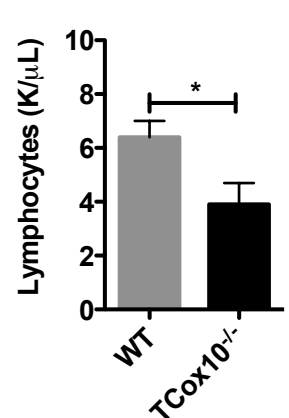
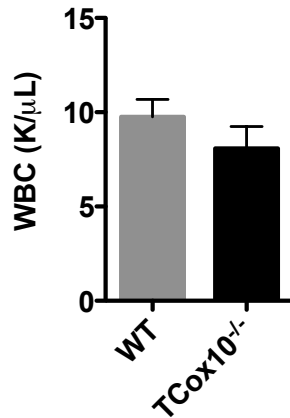
TCox10^{-/-} peripheral lymphocyte counts

Baseline

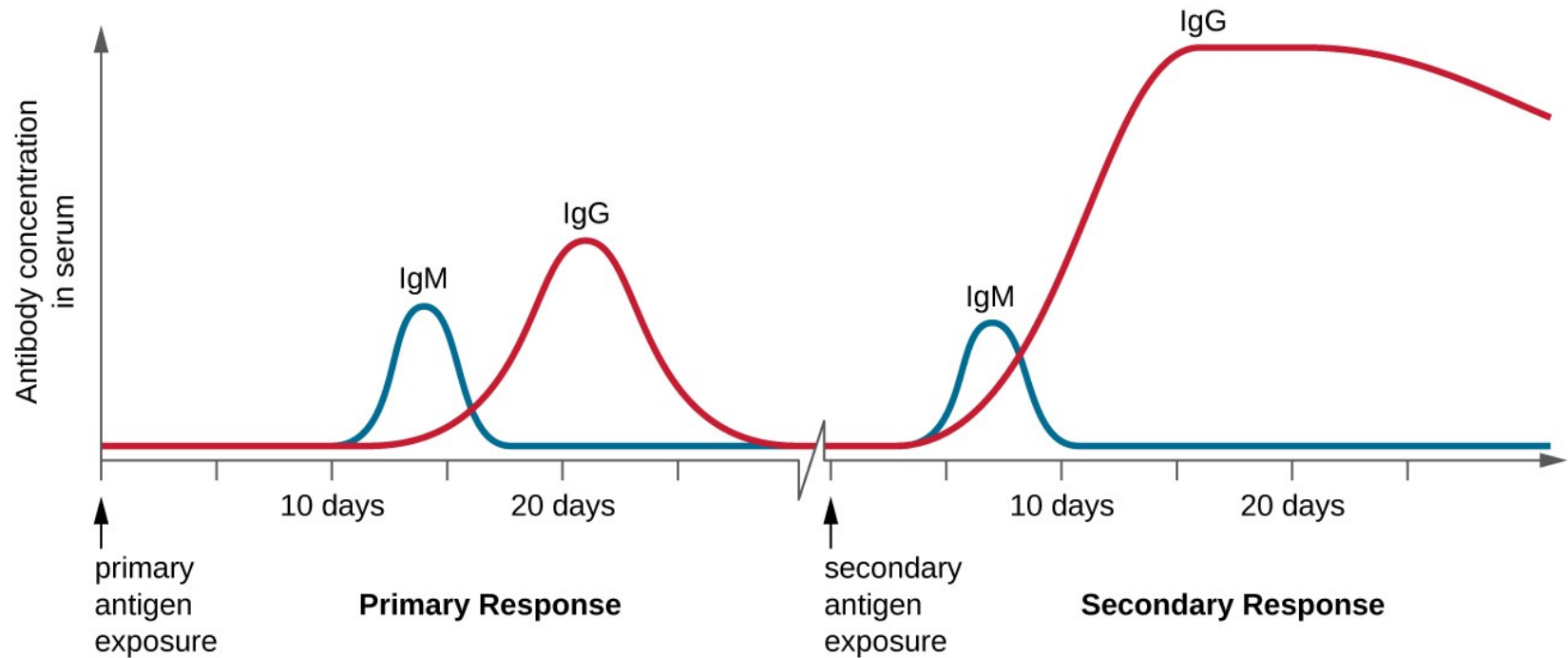


HEMAVET

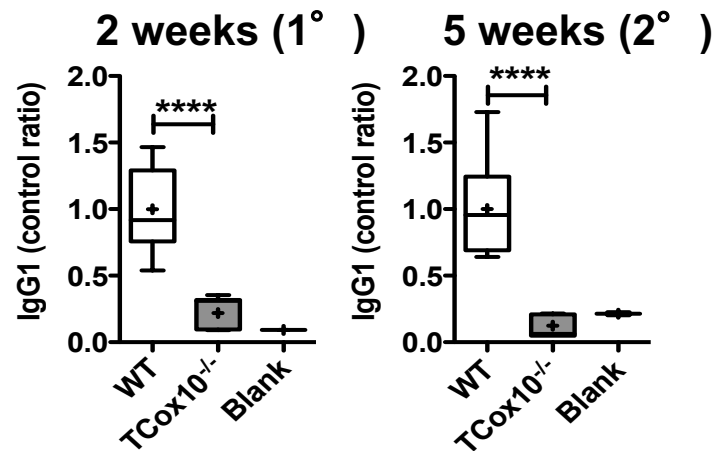
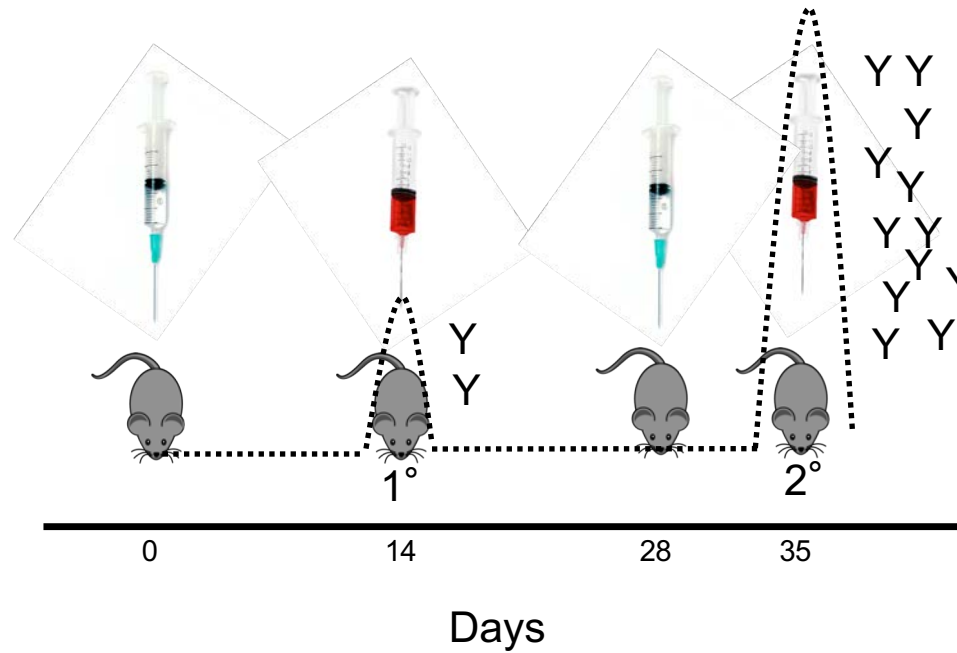
Infection



How does the immune system protect us?

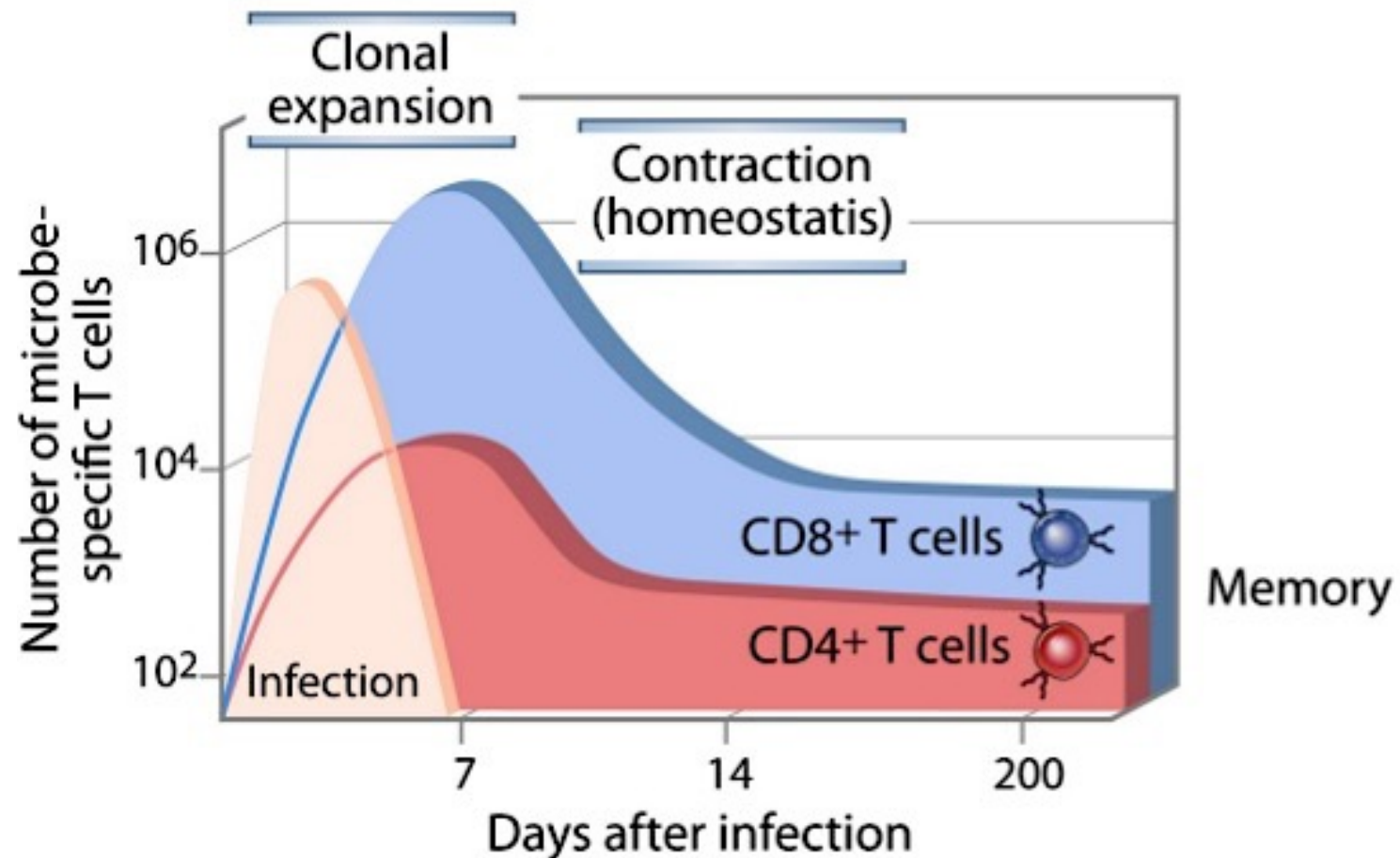


Vaccination response is impaired in TCox^{-/-}

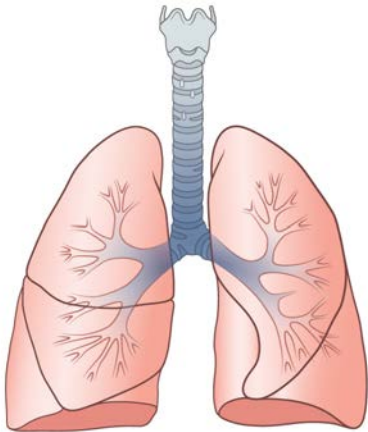
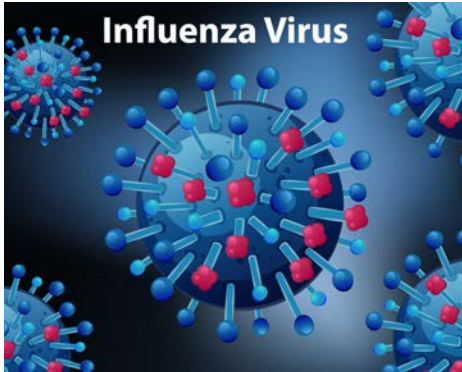
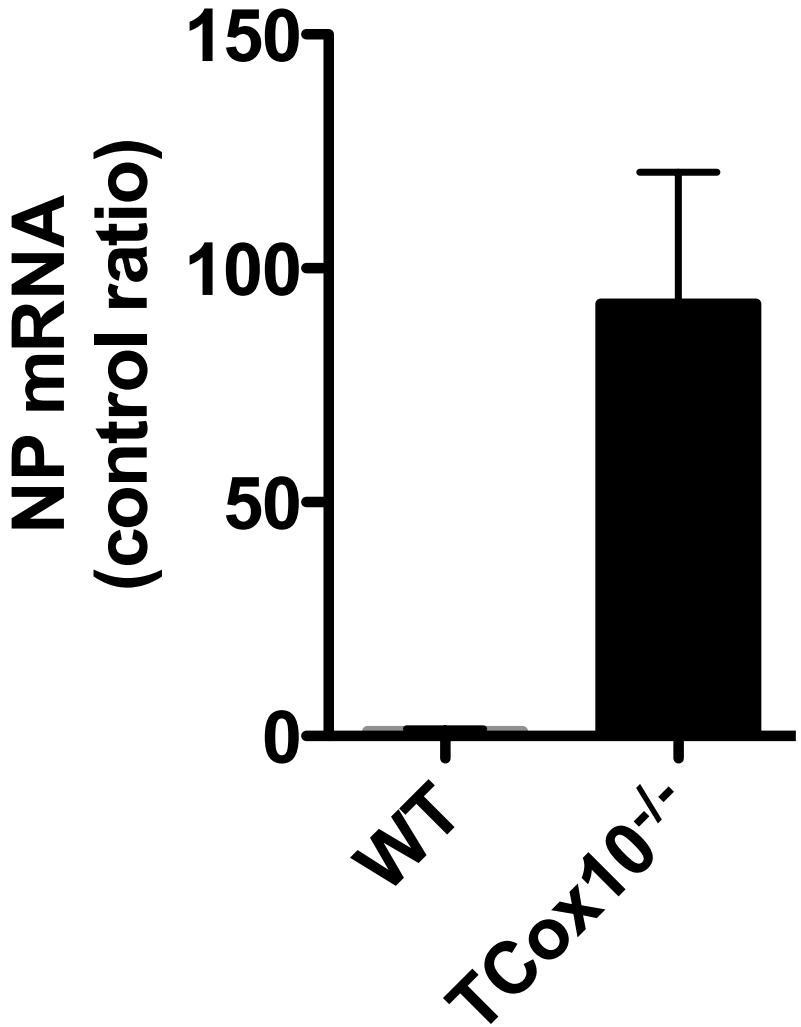


- **Clinical correlate:** loss of vaccine titers

How does the immune system protect us?



Influenza viral clearance is impaired in TCox10^{-/-}

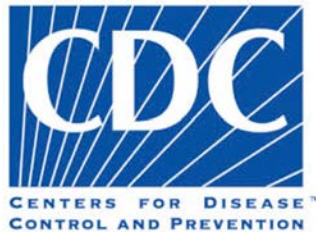


Summary

- The immune system is important for vaccination and protection against infection
- Infection may be detrimental to patients with MD
- Subsets of patients with MD may have immune dysfunction
 - Toxicity
 - Metabolic dysfunction

Longitudinal natural history study of immunity in MD

The NIH MINI Study: Metabolism, Infection, and Immunity in Inborn Errors of Metabolism (NCT01780168)



Goal:

- Mitigate risk in patients with MD
 - Identify immune susceptibilities and risks in patients with MD
 - Characterize organ systems which may be susceptible to dysfunction/damage during infection in MD



Travel, lodging and meals provided



Clinical Center

Children's Inn at NIH



The immune phenotype in patients with MD (NIH MINI Study)



Primary immunodeficiency
Allergic/Inflammatory diseases



Immune dysfunction



Stress-induced
immune dysfunction



Absent immune phenotype



Risk of decompensation

MINI Study contact information

Principal Investigator

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Staff Clinician

Eliza Gordon-Lipkin MD, PhD



Study Coordinator

Shannon Kruk, BSN, RN



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