National Academies of Sciences, Engineering & Medicine

The Evidence Base for Lyme Infection-Associated Chronic Illnesses and Treatment
Committee Meeting #3, Session I

Pathogen Persistence and Host Immune Response

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Ticks, Borrelia and Lyme Disease

Evolutionary problem:

No transovarial transmission of *Borrelia burgdorferi* from infected adult tick to egg

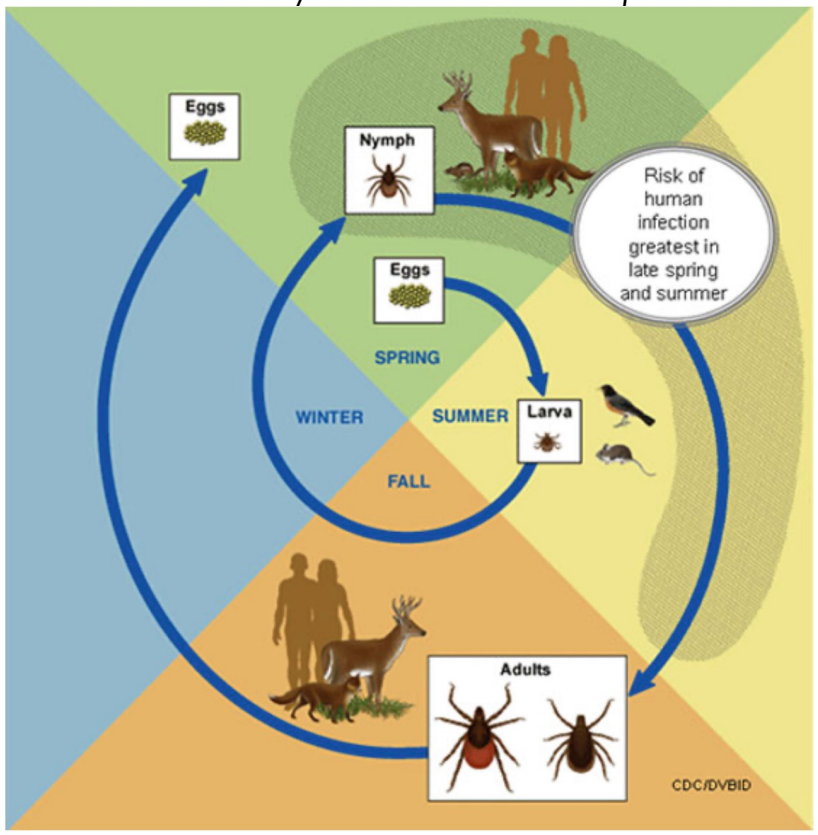
Survival in nature requires:

"Reservoir" host for spirochetes:
small rodents, birds, lizards

Deer (in North America) to support Ixodes tick reproduction

Telford & Goethert, Curr Issues Mol Biol 2021:42:267-306

Two –Year Life Cycle of *Ixodes scapularis* Ticks



Cultured Borrelia ≠ Tick-Transmitted Borrelia

Cultured Borrelia

- No selection pressure
- Lose pathogenicity and infectivity with repeated passage
- "clonal" populations likely not genetically identical
- Can enrich for persisters

Tick-Transmitted Borrelia

- Tick selection pressure
  - Bottlenecks at midgut epithelium and hemocoel prior to salivary gland entry
- Changes in gene expression to permit host adaptation begin prior to entry into the animal
- Tick saliva facilitates pathogen transmission
- Tick-reservoir host life cycle selects for spirochete "fitness"

Animal Models to Study Borrelia Persistence: Experimental Factors Influencing Outcome

- ***Borrelia burgdorferi***
  - Origin and strain
  - Culture conditions
  - Method of tick infection
- **Method of Infection**
  - Inoculation of cultured Borrelia
  - Inoculum dose
  - Tick-transmission
  - Number of ticks
- **Animal model**
  - Species
  - Immune competency
  - Reservoir competency
    - Can the species transmit infection back to feeding ticks?
  - Experimental controls
- **Antibiotics**
  - Bacteriostatic vs bactericidal
  - Oral, parenteral
  - **Dosing/drug pharmacokinetics**
  - Stage of infection
- **Evaluation of Persistence**
  - In the animal
    - Culture, DNA/RNA, microscopy, immune response, xenodiagnosis with ticks
  - Are spirochetes viable and infectious?
    - Immunosuppression
    - Tissue transplant
    - Xenodiagnosis with culture positivity or transmission to new host

Interpretation of Studies

Consensus (?)

- Antigenic material and nucleic acids can be detected after antibiotic treatment of Borrelia infected animals
- Presence of viable, culturable, infectious spirochetes after antibiotics is a rare and inconsistent finding across studies
- When nucleic acids or rare spirochete, non-culturable forms are identified after antibiotics, there is no clear pathology directly associated with them
- **There is no animal model of PTLDS**

Verschoor, et al. Clin Microbiol Rev 2022 Dec 21;35(4):e0007422

Differences in Perspective

Evidence for Persistent Borrelia Antigens

Research article Related Commentary, page 2344

Spirochete antigens persist near cartilage after murine Lyme borreliosis therapy

Linda K. Bockenstedt,[1] David G. Gonzalez,[2] Ann M. Haberman,[2] and Alexia A. Belperron[1]

[1]Department of Internal Medicine and [2]Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut, USA.

Alan Barbour: "Remains of Infection"
J Clin Invest. 2012;122(7):2344-2346

Stages of Dying

- Loss of cell wall
  - Replication, reversion
- No cell wall
  - No replication or reversion
- Cell lysis or immune breakup
  - Blebs or vesicles containing DNA, protein
- Degradation
  - DNA degrades, protein remains

Borrelia burgdorferi peptidoglycan is a persistent antigen in patients with Lyme arthritis

Brandon L. Jutras[a,b,c,1], Robert B. Lochhead[d,2], Zachary A. Kloos[a,e], Jacob Biboy[f,g], Klemen Strle[d], Carmen J. Booth[h], Sander K. Govers[a,b], Joe Gray[i], Peter Schumann[j], Waldemar Vollmer[f,g], Linda K. Bockenstedt[k], Allen C. Steere[d], and Christine Jacobs-Wagner[a,b,c,l,3]

PNAS 2019; 116(27) 13498-13507

RESEARCH Open Access

Peptidoglycan in osteoarthritis synovial tissue is associated with joint inflammation

Meaghan N Holub[1,2], Amanda Wahhab[2], Joseph R Rouse[2], Rebecca Danner[2], Lauren G Hackner[2], Christine B Duris[3], Mecaila E McClune[4,5,6], Jules M Dressler[4,5], Klemen Strle[7], Brandon L Jutras[4,5,6], Adam I Edelstein[8*] and Robert B Lochhead[1,2,9*]

Clin Rheumatol (2012) 31:989–994
DOI 10.1007/s10067-012-1964-x

ORIGINAL ARTICLE

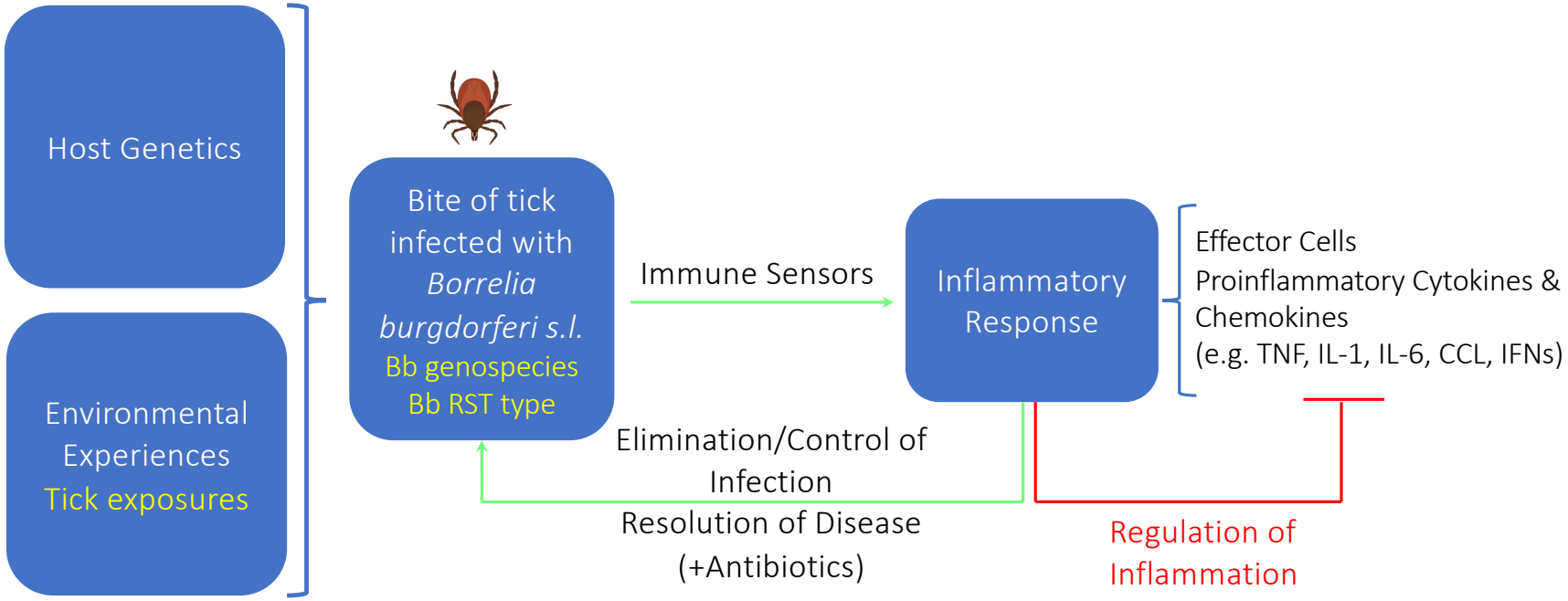
The amber theory of Lyme arthritis: initial description and clinical implications

Gary P. Wormser · Robert B. Nadelman · Ira Schwartz

PART 2:

Host Response & Post-Treatment Complications of Lyme Disease

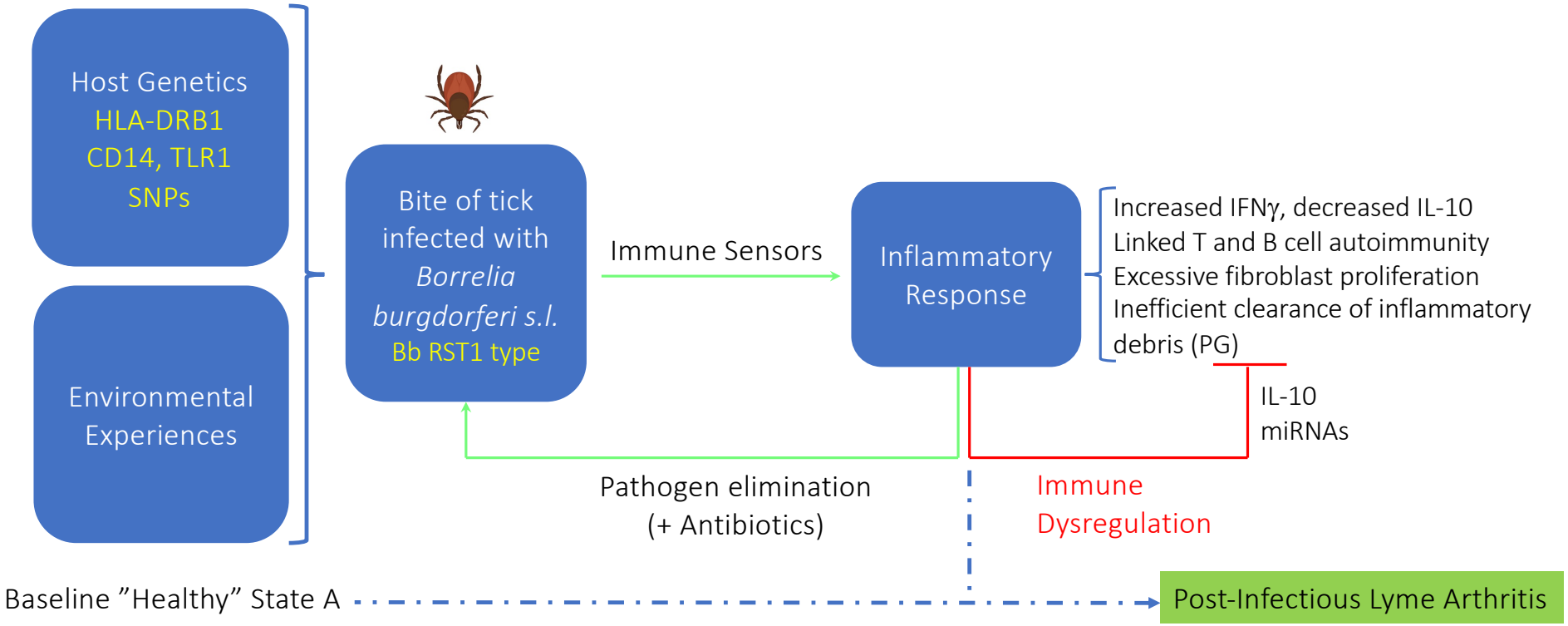
Host Response in Lyme Disease



Lyme Arthritis: A Late Manifestation of Infection

- Occurs months after infection
- Adult patients typically do not remember an acute illness suggestive of infection with *Borrelia burgdorferi*
- Strong seropositivity is the rule
- Treatment of the primary infection has been delayed by many months
- The vast majority respond to IDSA-recommended courses of antibiotics
- PCR positivity in joint fluid after institution of antibiotics does not correlate with outcome of treatment

Outcome: Post-Infectious Lyme Arthritis



Lochhead, et al Nat Rev Rheumatol 2021;17(8):449-461
Jutras, et al PNAS 2019; 116(27) 13498-13507

Outcome: Post Treatment Lyme Disease Syndrome

Major Clinical Symptoms

- Fatigue
- Musculoskeletal pain
- Cognitive issues

Risk Factors

- Severity of symptoms at the time of treatment
- Presentation with multiple EM

Autoimmunity
Anti-neuronal antibodies

Chandra, et al. Brain Behav Immun 2010;24:1018-1024
Jacek, et al. J Neuroimmunol 2013; 255:85-91
Fallon, et al. Brain Behav Immun Health 2020; Feb; 2: 100015

Elevated Cytokines
IL-23, IFNα

Strle, et al. Clinical Infect Dis 2014; 58:372-380
Jacek, et al J Neuroimmunol 2013; 255:85-91
Hernandez, et al. Emerging Infect Dis 2023; 29(6):1091-1101

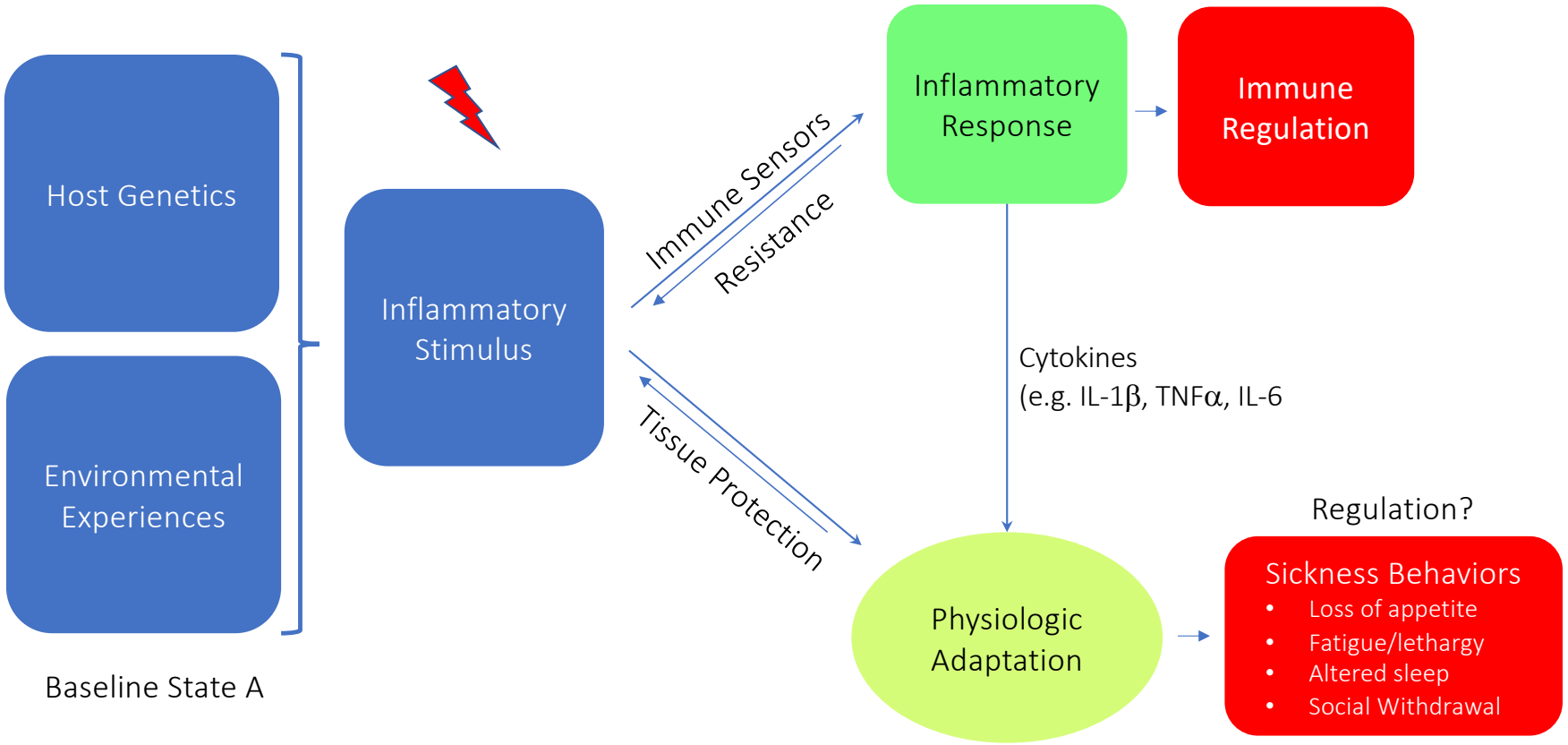
Lower Initial Plasmablast

Blum, et al. Front Immunol 2018; 9:1634

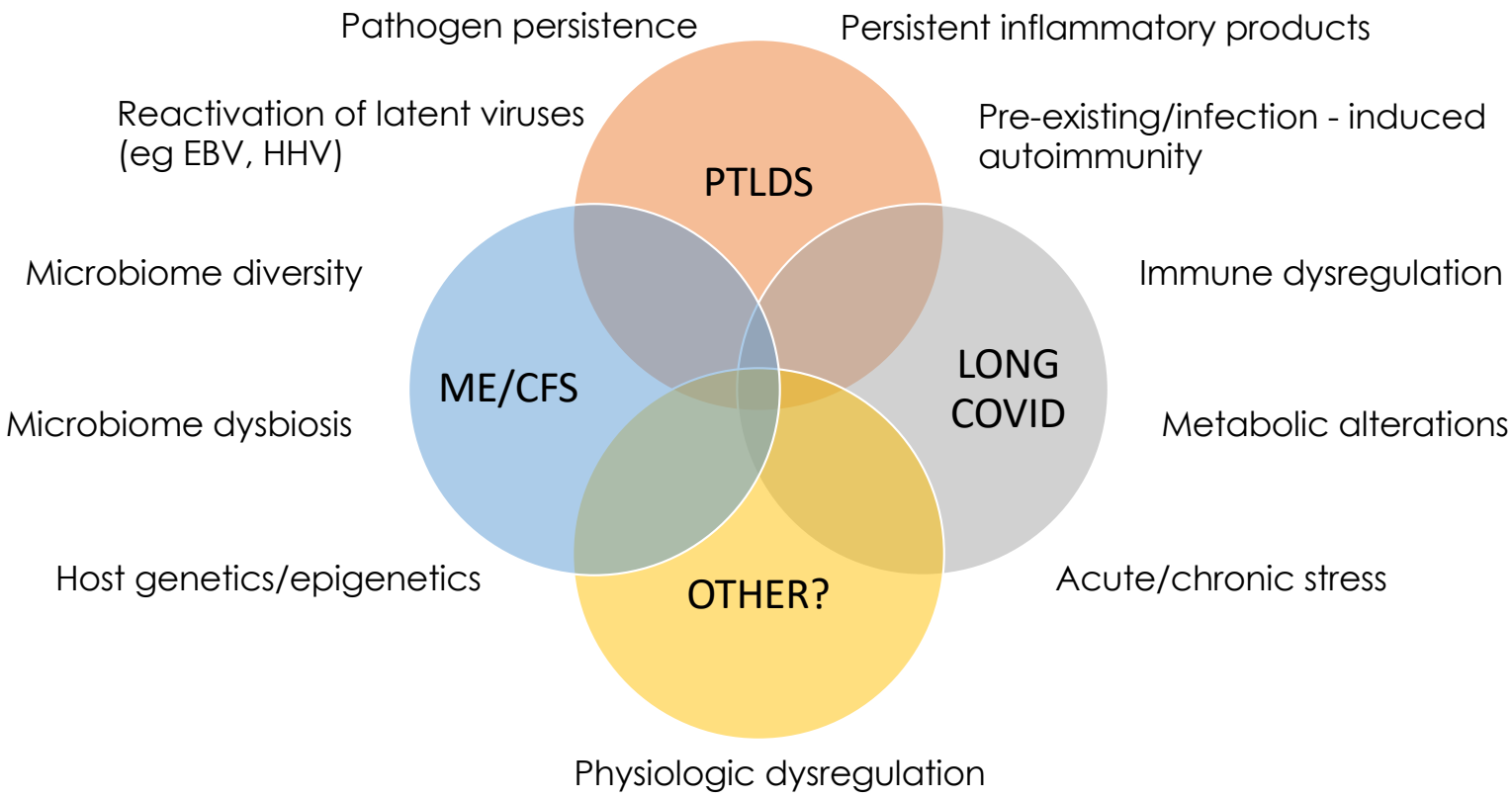
Metabolic Signature

Fitzgerald, et al. Clinical Infect Dis 2021; 73(7):e2342-e2349

Host Response to Immune Challenges



Research Opportunities



Research Design Opportunities to Understand Pathogenesis

- Standardize case definitions
- Define subcategories
- Use common terminology for data collection
- Apply a multitude of modern analytic tools/technologies
- Make use of available centralized knowledge bases and resources
- Engage experts outside the field

Questions?