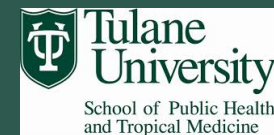




Long-Lyme:

Immune Responses in Effective Diagnosis & Treatment of Lyme disease

Monica E. Embers, Ph.D.

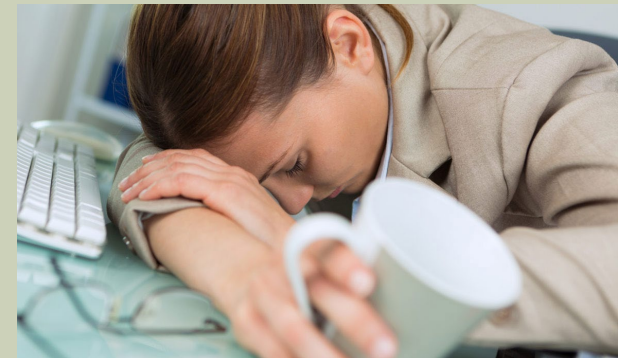
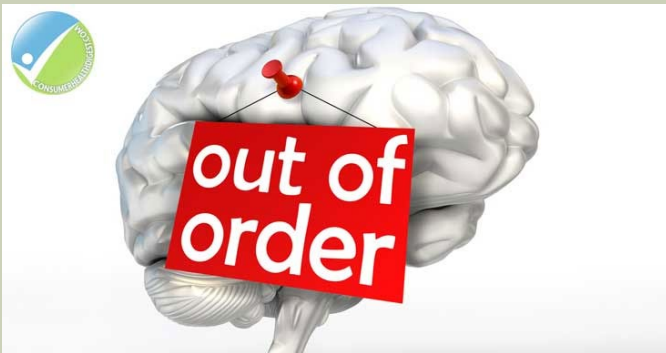


Tulane
SCHOOL OF MEDICINE

POST-TREATMENT LYME DISEASE (PTLD)

- **Potential causes include:**

- **Induction of inflammatory responses by lingering dead spirochetes or spirochetal antigen**
- **Continuation of active spirochetal infection**
- **Irreversible sequelae from previous active infection (autoimmune)**



Inflammatory infiltrates and antimicrobial-tolerant persistent *B. burgdorferi* in tick-inoculated rhesus macaques 8 to 9 months after treatment with oral doxycycline



Borrelia burgdorferi Antimicrobial-Tolerant Persistence in Lyme Disease and Posttreatment Lyme Disease Syndromes

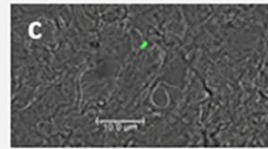
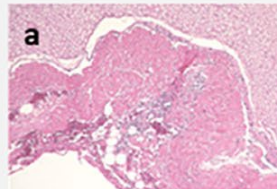
● Felipe C. Cabello,* ● Monica E. Embers,* ● Stuart A. Newman,* ● Henry P. Godfrey**

*Department of Pathology, Microbiology and Immunology, New York Medical College, Valhalla, New York, USA

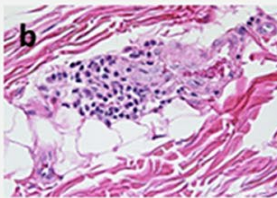
**Department of Cell Biology and Anatomy, New York Medical College, Valhalla, New York, USA

†Division of Immunology, Tulane National Primate Research Center, Tulane University Health Sciences, Covington, Louisiana, USA

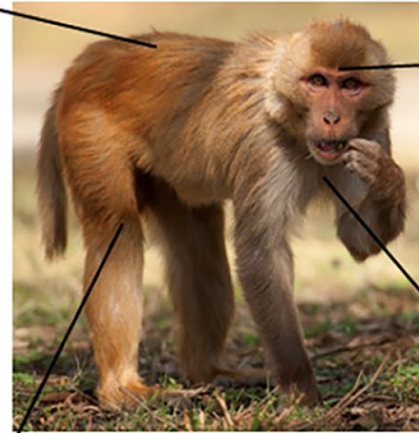
A. Spinal and peripheral nerves



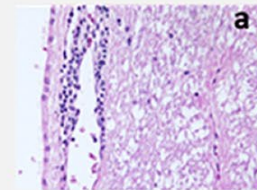
Persistence



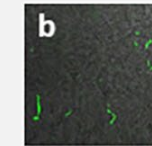
Inflammation



B. Brain and meninges

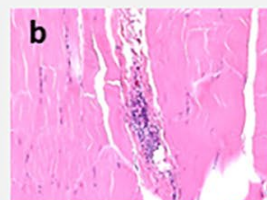
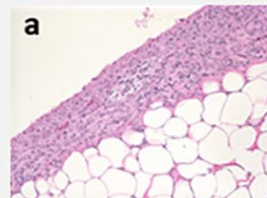


Inflammation

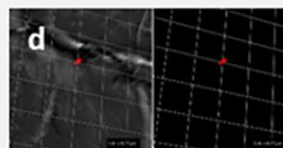
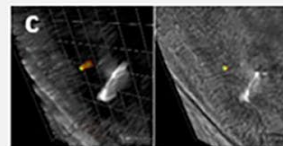


Persistence

C. Joints and skeletal muscle

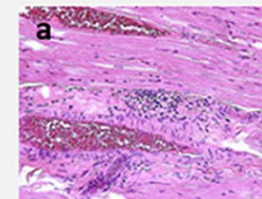


Inflammation

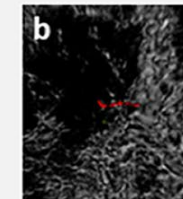


Persistence

D. Heart



Inflammation



Persistence



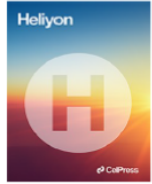
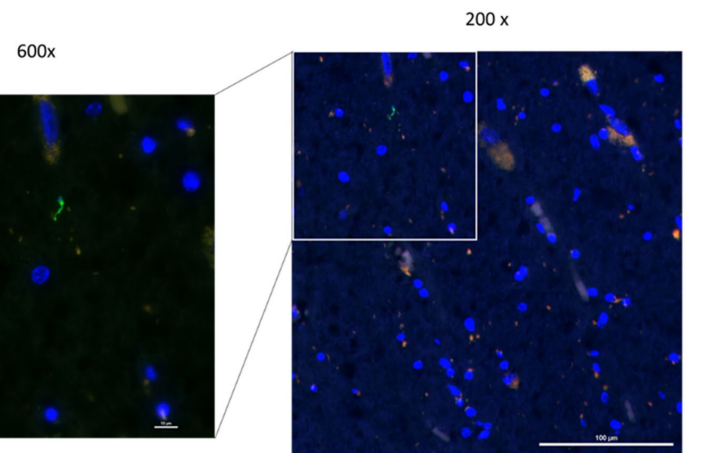
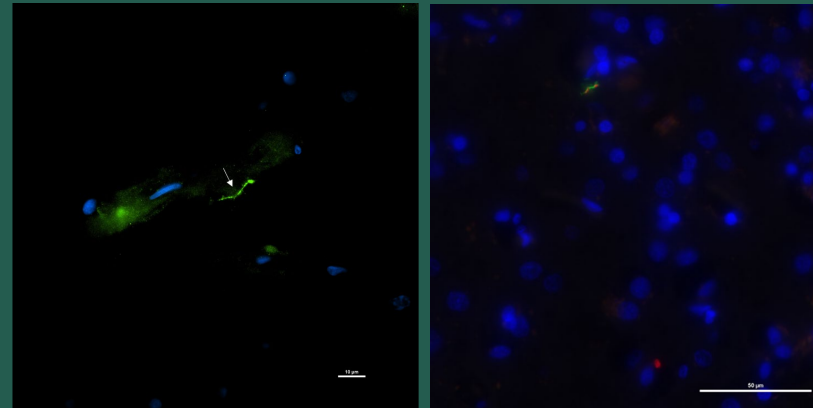
Persistence (from *in vivo* culture)



Detecting Borrelia Spirochetes: A Case Study With Validation Among Autopsy Specimens

Shiva Kumar Goud Gadila¹, Gorazd Rosoklija^{2,3}, Andrew J. Dwork^{2,3,4,5}, Brian A. Fallon^{2*} and Monica E. Embers^{1*}

¹ Division of Immunology, Tulane National Primate Research Center, Tulane University Health Sciences, Covington, LA, United States, ² Department of Psychiatry, Columbia University, New York, NY, United States, ³ Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, NY, United States, ⁴ Macedonian Academy of Sciences and Arts, Skopje, Macedonia, ⁵ Department of Pathology and Cell Biology, Columbia University, New York, NY, United States



Case report

Late-stage borreliosis and substance abuse

Robert C. Bransfield^a, Shiva Kumar Goud Gadila^b, Laura J. Kursawe^c, Andrew J. Dwork^{d,e,f,g}, Gorazd Rosoklija^{e,g}, Elizabeth J. Horn^h, Michael J. Cookⁱ, Monica E. Embers^{b,*}

^a Rutgers-RWJ Medical School, Piscataway, NJ, USA. Hackensack Meridian Health-School of Medicine, Nutley, NJ, USA

^b Division of Immunology, Tulane National Primate Research Center, Tulane University Health Sciences, Covington, LA, USA

^c Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117, Berlin, Germany

^d Department of Psychiatry, Columbia University, New York, NY, United States. Division of Molecular Imaging and Neuropathology, New York, USA

^e State Psychiatric Institute, New York, NY, USA

^f Macedonian Academy of Sciences and Arts, Skopje, Macedonia

^g Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

^h Lyme Disease Biobank, Portland, OR, USA

ⁱ Independent Researcher, Dorset, BH23 5BN, UK

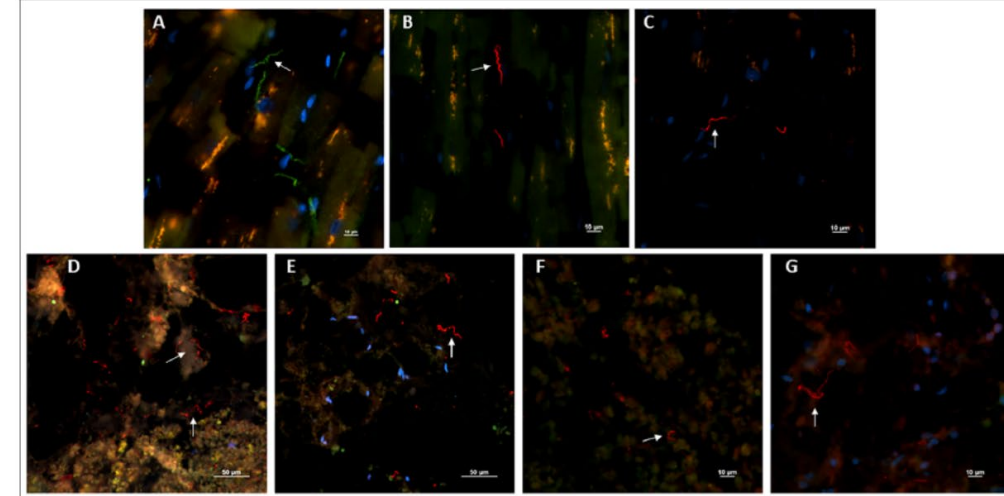


Fig. 3. Immunofluorescent antibody-based detection of spirochetes in the heart and pancreas. Heart tissues (A,B,C) and pancreas tissue (D,E,F,G) from FFPE sections were stained with: (A) chicken anti-FlaB primary followed by Alexa-488 secondary; (B,C,D,E) Rabbit antisera against BipA of *B. burgdorferi* followed by Alexa-594; and (F,G) rabbit antisera against *B. burgdorferi* followed by Alexa-594. White arrows point to some of the multiple spirochetes. Orange/yellow staining reflects tissue autofluorescence. Scale bar = 50 μ m. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

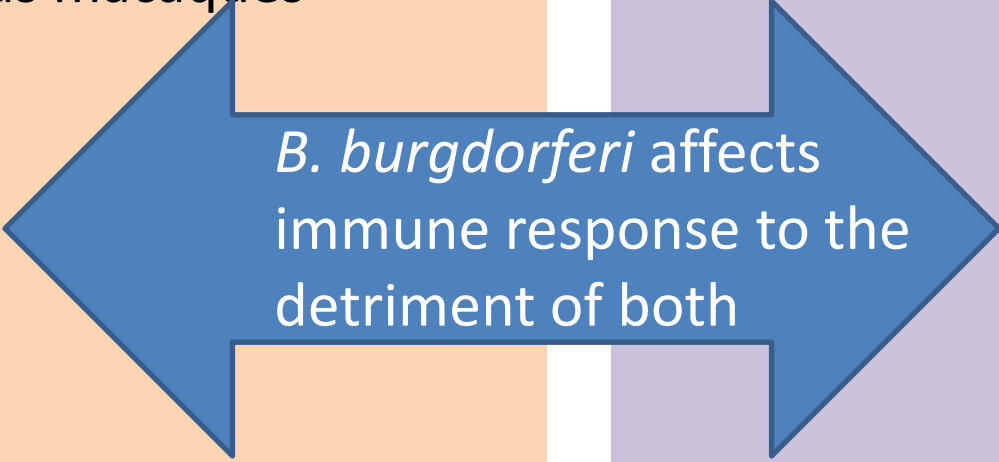
Lyme Borreliosis Research

- **Diagnosis**

- Longitudinal assessment of antibody responses/variability in rhesus macaques

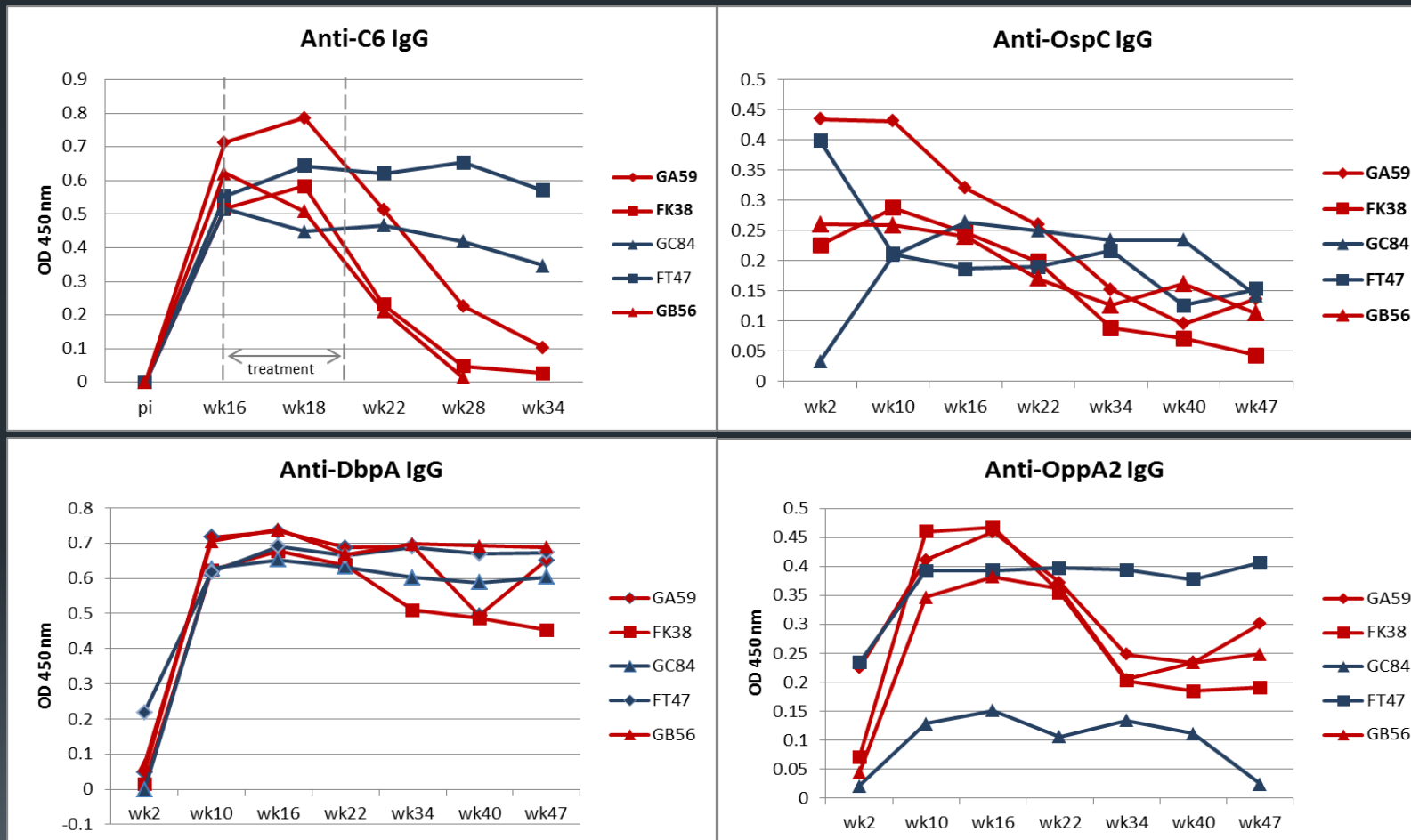
- **Treatment**

- Examination of responses of individuals with clinical cure vs. those with PTLDS



B. burgdorferi affects immune response to the detriment of both

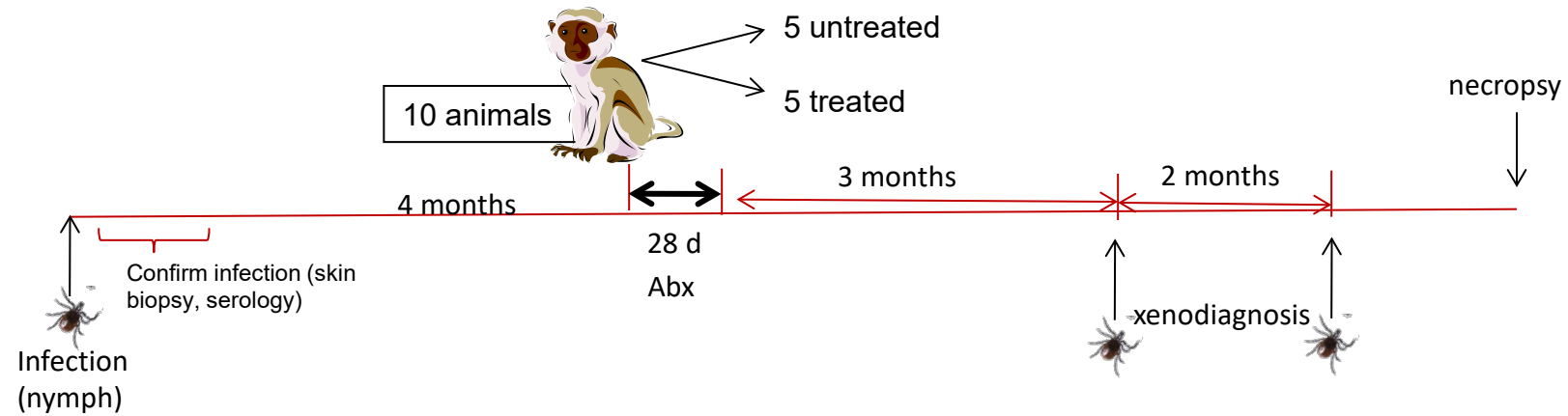
How do immune responses change over the course of infection and post-treatment?



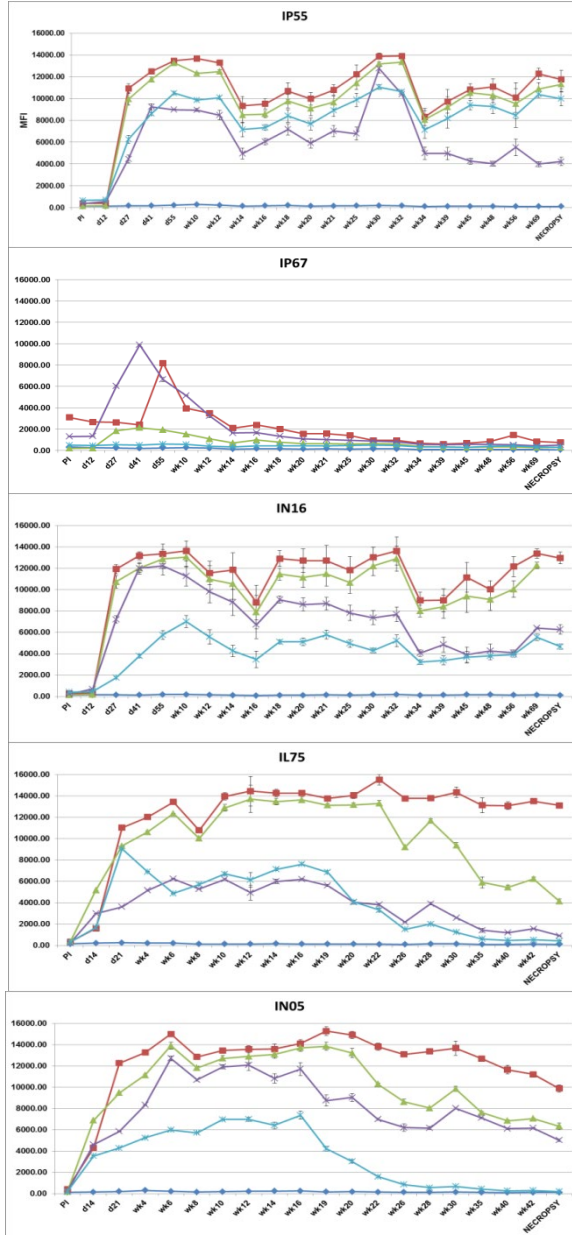
Anti-C6, OspC, DbpA and OppA2 IgG antibody responses from 5 monkeys:
3 treated at 4 months post-infection and 2 untreated.



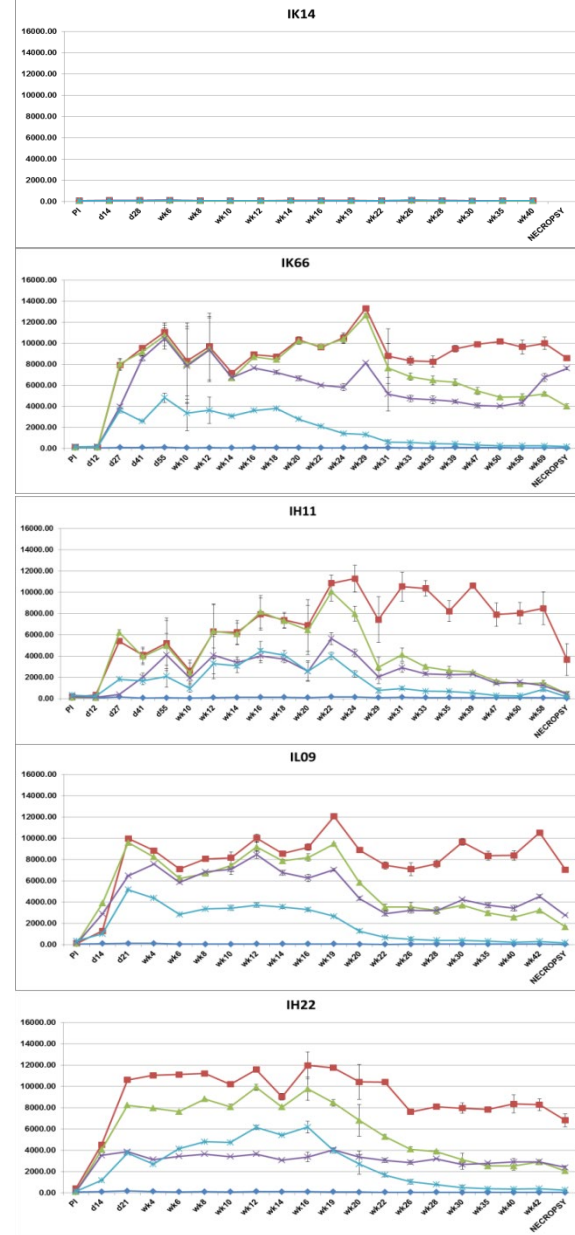
Variable antibody responses in primates: tick-mediated infection, treatment, and evaluation for persistent infection



UNTREATED



TREATED



● OspA
 ■ DbpA
 ▲ OppA-2
 × OspC
 * C6

Antibody responses
 to five different Bb
 antigens over 60
 weeks following
 infectious tick bite.
 Antibody responses
 by **untreated** animals
 and animals **treated**
 with **doxycycline**
 between **weeks 16-20**
 are shown. All values
 shown are triplicate
 averages with the
 mean pre-immune
 value per individual
 animal subtracted.

Variable antibody responses among human Lyme disease patients:

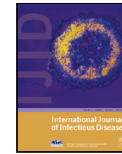
International Journal of Infectious Diseases 17 (2013) e443–e449



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journal homepage: www.elsevier.com/locate/ijid



Development of a foundation for a case definition of post-treatment Lyme disease syndrome

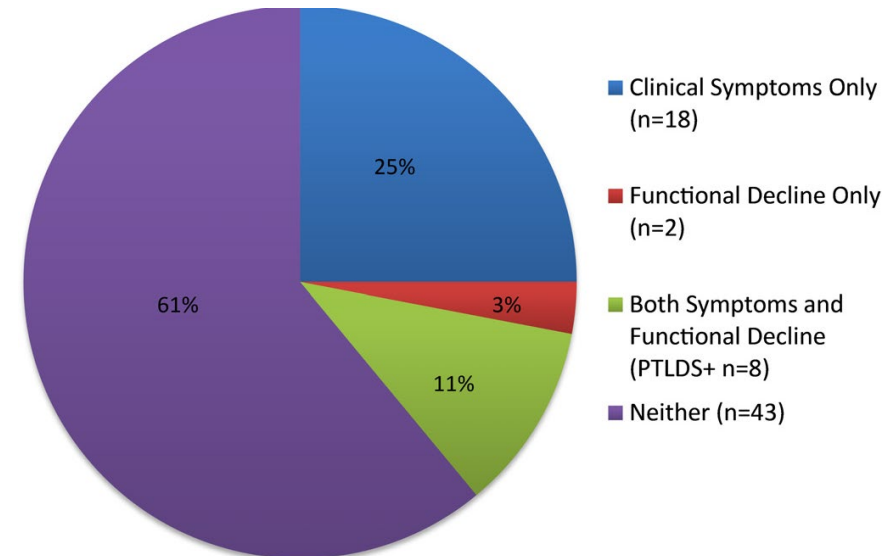
John N. Aucott^{a,*}, Lauren A. Crowder^b, Kathleen B. Kortte^c

^a Department of Medicine, The Johns Hopkins University School of Medicine, 10755 Falls Road, Suite 200, Lutherville, MD 21093, USA

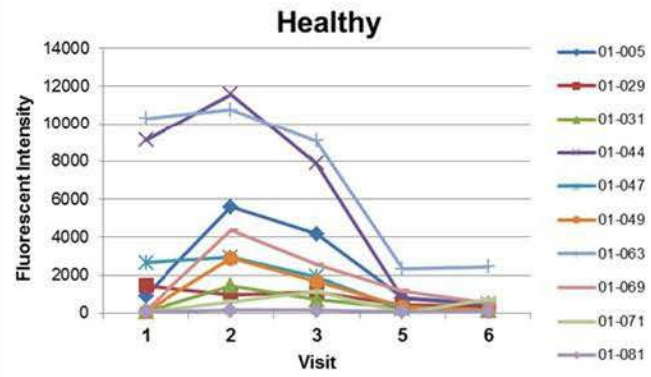
^b Lyme Disease Research Foundation, Lutherville, Maryland, USA

^c Department of Physical Medicine and Rehabilitation, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

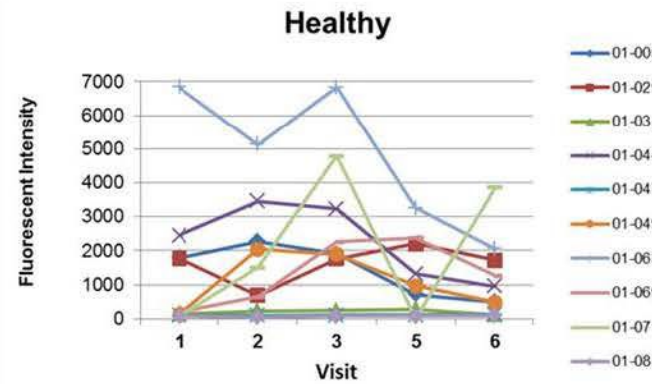
Test for differences in specific antibody between cured and PTLDS patients



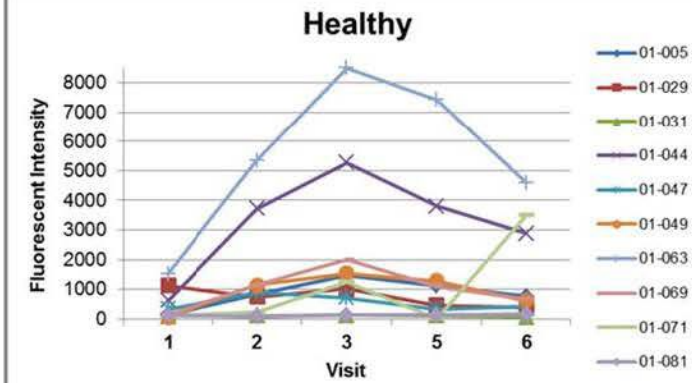
Anti-C6 IgG



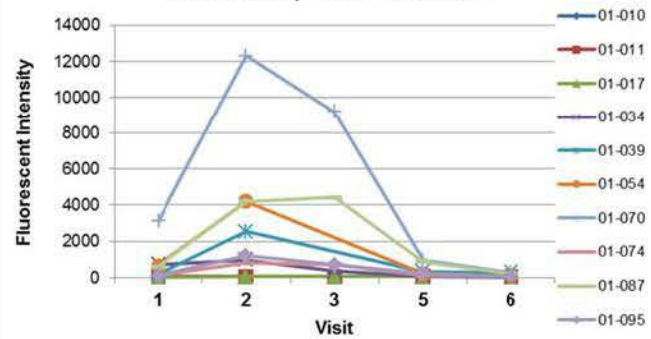
Anti-OspC IgG



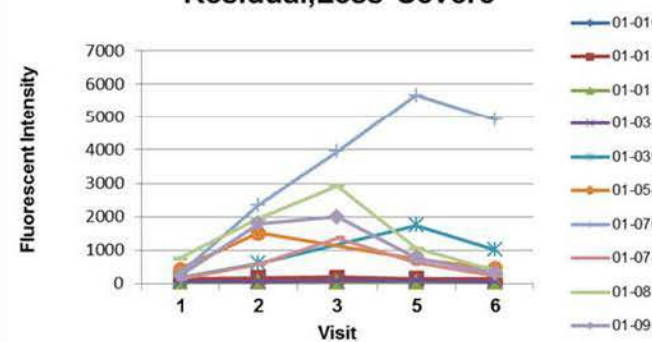
Anti-DbpA IgG



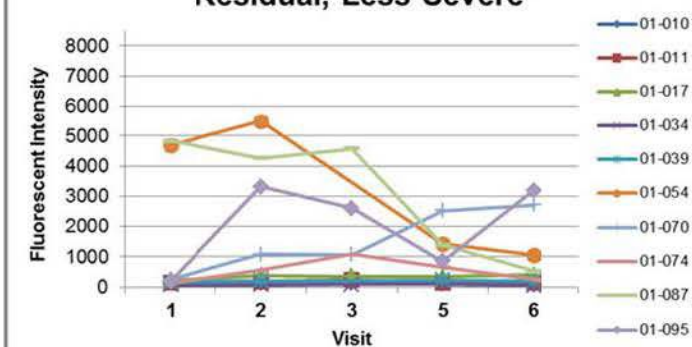
Residual, Less Severe



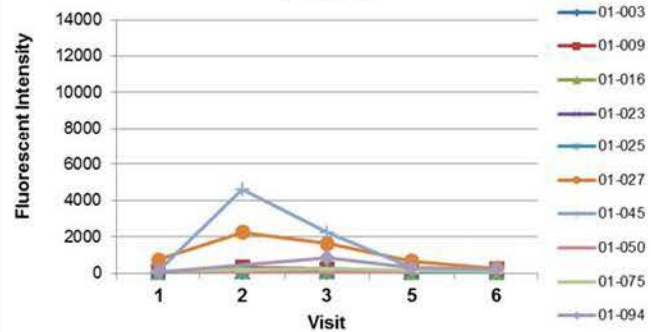
Residual, Less Severe



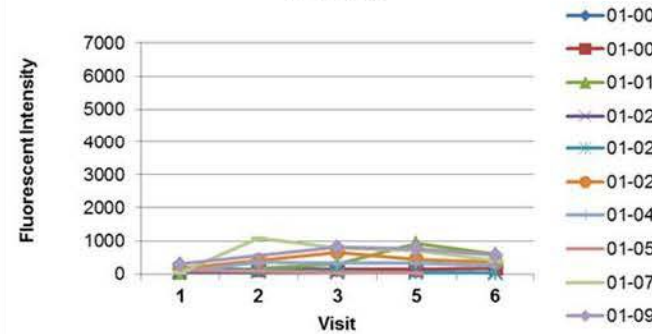
Residual, Less Severe



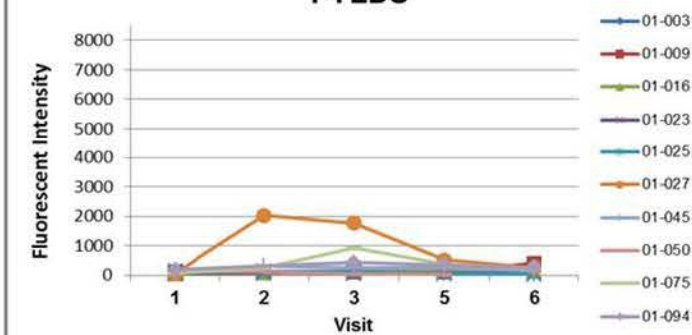
PTLDS



PTLDS



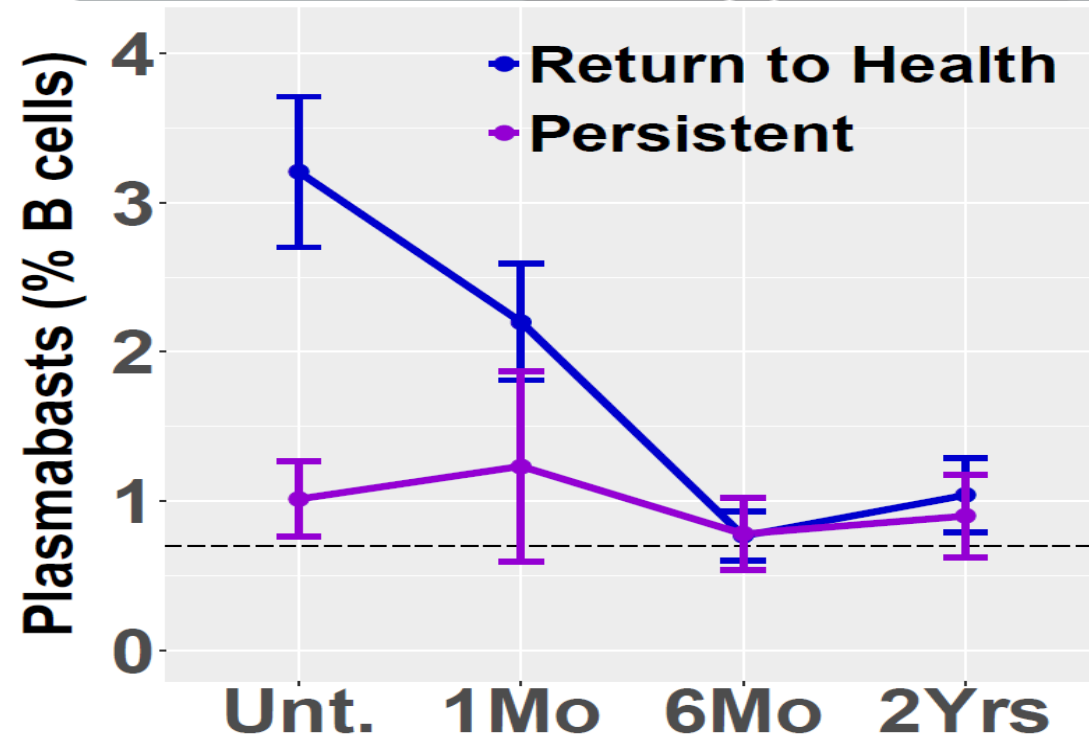
PTLDS



The effect of immune response on treatment outcome

Robust B cell responses predict resolution of symptoms in Lyme disease

Authors: Lisa K. Blum, Julia Z. Adamska, Dale S. Martin, Alison W. Rebman, Serra E. Elliott, Richard R.L. Cao, Monica E. Embers, John N. Aucott, Mark J. Soloski, William H. Robinson



- ☐ **Host antibody responses appear to be predictive of clinical cure**
- ☐ **Responses vary by antigen used to detect infection and over time**
- ☐ **Commonly used antibiotics (doxycycline, amoxicillin) don't kill pathogen**

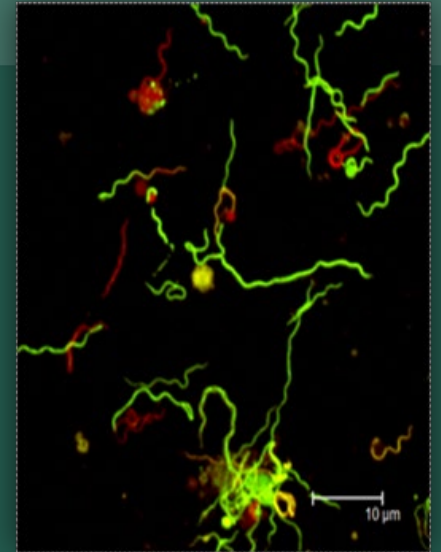


Possible explanations for weak responses:

- 1. Host differences in the ability to generate humoral response to Bb (possibly in isotype switching)**
- 2. Strain differences among Bb and/or co-infections influence host immunity**

Key research gaps and needs for the field

- A serological test that detects infection at all stages of infection/disease.
- A reliable indicator of treatment outcomes (to distinguish persistent infection from other causes of PTLD)
- Determine how genetics and co-infection influence immunity to infection with *Borrelia*
- Clinical trials of new treatment regimens using combinations of antibiotics



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Havard Lambert
Celine McDaniel

THANK YOU



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Liz Didier, PhD

Veterinary Medicine
Lara Doyle, DVM
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Pathology
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Pete Didier, DVM, PhD

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(pathologist)
Dr. Brian Fallon
Dr. Gorazd Rosoklija

Lyme Disease Biobank
Dr. Liz Horn



GLOBAL LYME ALLIANCE
Conquering Tick-borne Disease through Research & Education



Bill & Marian Cook Foundation