Conquering Lyme Disease: Science Bridges the Great Divide
We have Lyme Disease and we need Help! ...please.
“Throwing Weight Around” by David Skidmore

CHRONIC LYME

NO CHRONIC LYME
Bless us for thy bounty for which we are about to receive.

...From Bob.

Ticks preparing for a human blood meal

By David Skidmore
Major Periods in the History of Lyme Disease

- 1976-1990 Discovery & Openness
- 1990-2008 Narrow Definitions, Conflict & Entrenchment
- 2008- Renewed discovery & exploration
A brief history of Lyme disease...

3000 BCE
Ice Man: Lyme DNA 5,000 yrs old

1980
Spirochete found in tick

1990
"Lyme: The NEW great imitator"

CDC 2-Tier Criteria


Persistence of Bb in Animal Models after Abx treatment

2000
Vaccine

2010
Systems Biology – "-Oomics"

2015
>300,000 new diagnoses/yr

Graph showing estimated and confirmed cases of Lyme disease from 1993 to 2013.
The efforts of mothers, families, and patients have advanced the research through funding and awareness.

Polly Murray

Lyme Disease Foundation, Inc.
Finding solutions to tick-borne disorders since 1983

Time for Lyme

Tick-Borne Disease Alliance

Turn the Corner - The Fight Against Lyme Disease

Global Lyme Alliance

CALDA

lymedisease.org

Lyme Disease Association

National Research Fund for Tick-Borne Diseases, Inc.

GIVE

Patients & Parents Mobilize
Paradigm Shifts of last decade

- Recognition that Lyme Disease is not simple
  - Current blood tests are inadequate
    - Only 35-50% sensitive in early Lyme disease
  - Spirochetes can persist – even after standard antibiotic treatment – a new focus of research

- Recognition that chronic symptoms have biological correlates (in the brain, spinal fluid, & blood)
Paradigm Shifts of last decade

- Recognition: an epidemic
  - The geographic spread of ticks is expanding

- Discovery of new microbes in the ticks

- Recognition of the brain’s involvement in persistent symptoms.
Technology Advances – Genome sequencing is now fast & inexpensive: cost up to $1 billion in 1999-2003

CURRENT COST: ~$1,000
Technology Advances: new assays & biomarkers - the power of OMICS

- Genomics
- Transcriptomics
- Proteomics
- Epigenomics
- Metagenomics
- Metabolomics
- Nutriomics

Omic Profile

Microbiome
Neural Connectome

Personalized Medicine

- Data Integration, Analysis & Interpretation
- Systems Biology
- Bioinformatics
- Biomathematics
- Biostatistics

Complex Disease Networks

Patient-Specific Interactions

Clinical Care Innovations

Care Delivery
Patient Education

Alyssa, et al., 2015, BMC Medical Genomics 8:33
Intriguing Images
Borrelia spirochetes persist despite antibiotics. This has been shown in many species.

Often with minimal or No Disease

Slide courtesy of Stephen Barthold, UC Davis
Spirochetes can be visualized within tissue of a mouse at 12 months following antibiotic treatment.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0086907
Persistence of B burgdorferi in the Rhesus Macaque

Monica Embers, Tulane University
The human xenodiagnostic study
(Marques et al, CID, 2014)

- Tick from 1 of 9 persons with previously treated Lyme Disease tested positive by PCR for DNA of the Lyme spirochete.
Advances: Metagenomic Next Generation Sequencing enable rapid detection of All Microbes

Bacteria

Viruses

Fungi

Parasites

Turn around time: hours to days (vs. days – weeks)

Allows one to cast a wide net to discover all microbes – not just a single fishing pole/guess to catch one microbe
Advances: Cell-based assays become negative after treatment – marker of cure?

- Assesses cytokine response to Lyme protein stimulation of human T-cells (or macrophages)

- In early Lyme Disease (EM) (Callister 2016):
  - 69% sensitivity
  - After treatment (2 months later) – 80% negative
Advances in Diagnosis: Metabolomics-based assay

metabolic biosignature: sugars, peptides, lipids, nucleic acids

**Early Lyme vs Controls** (Molins et al, 2015)

- 88% sensitive in early Lyme (2x higher than 2-Tier assay)
- Differentiates Lyme from other diseases
  - Correct differentiation 93% of Lyme from CFS & Fibromyalgia

Next: study **Post-treatment Lyme disease** using Metabolomics

- To identify a biosignature of recovery and of PTLDS
- To suggest new treatments
Causes of Persistent symptoms under investigation

Persistent Bb infection

Unrecognized Coinfections

Neural Network dysregulation

Immune dysregulation

Causes of Persistent symptoms under investigation

- Persistent Bb infection
- Unrecognized Coinfections
- Immune dysregulation
- Neural Network dysregulation

Advance: repeated antibiotic therapy can help persistent fatigue. Columbia & Stonybrook NIH Studies

% Responders

- Ceftriaxone
- Placebo

Krupp 2003 All patients
Krupp 2003 IgG WB+ patients
Fallon 2008
Advance: Persister Borrelia require different approaches for eradication

Ying Zhang, MD (Hopkins)  Kim Lewis, PhD (Northeastern)
Advance: ticks carry more than just the agent of Lyme disease

- Borrelia miyamotoi
- Borrelia mayonii
- Babesia Microti
- Anaplasma phagocytophylum
- Ehrlichia
- Powassan Virus

Rafal Tokarz
Advance: Recognition that Lyme disease leads to an altered Cerebrospinal Fluid protein profile (692 unique proteins)

- This proteomic CSF profile differentiated post-treatment Lyme disease from Chronic Fatigue
- Persistent symptoms are associated with an increase in immune proteins

Advance: recognitions that patients with chronic Lyme symptoms have objective brain changes: altered brain metabolism & blood flow. (Columbia Imaging studies)

The patient group showed a diminished ability to enhance blood flow compared to controls (8.2% for patients vs 28.1% for controls, p<.02) (Fallon et al, JAMA Psychiatry, 2009)
Current research: Do human post-mortem brains from LD harbor Lyme spirochetes?

- Columbia
  - Andrew Dwork
  - Gorazd Rosoklija
  - Jim Goldman
  - Brian Fallon

- Tulane:
  - Monica Embers

- Southern Research Institute/GLA
  - Tim Sellati

- Collaborators
  - Ken Liegner
  - Judith Miklossy

Monkey Brain Tissue
Current Research: Are the brain’s neural circuits or chemistry altered? A Columbia study of Post-treatment Lyme patients

Functional Magnetic Resonance Imaging
- Does the brain show central sensitization – hyperactivated pain circuits compared to healthy controls?

Magnetic Resonance Spectroscopy
- Is the brain neurochemistry different from healthy controls?

Alla Landa, PhD
Prevention is key
What is the patient’s experience?

Eduard Munch: Sensory Hyperarousal

William Blake: Job Being Accused
New Columbia Lyme Center
Pediatric Research Outreach

- Joining forces with Columbia Neurology
- Focus on infection-triggered and immune-triggered neuropsychiatric disorders

Shannon Delaney (Child Psychiatry), Wendy Vargas (Pediatric Neurology), Dritan Agalliu (Neurology, Pathology, Cell Biology)
So.....is there reason for hope?
Yes, Science is creating a bridge across the great Lyme Divide
CONQUERING LYME DISEASE

SCIENCE BRIDGES THE GREAT DIVIDE

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All Royalties support research
THANK YOU TO OUR DONORS, FUNDERS, & COLLABORATORS

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DEPARTMENT OF PSYCHIATRY
College of Physicians and Surgeons

GIVE
STEVEN & ALEXANDRA COHEN FOUNDATION

NIH
National Institutes of Health
Turning Discovery Into Health
Thank you from our team

Columbia Lyme & Tick-Borne Diseases Research Center