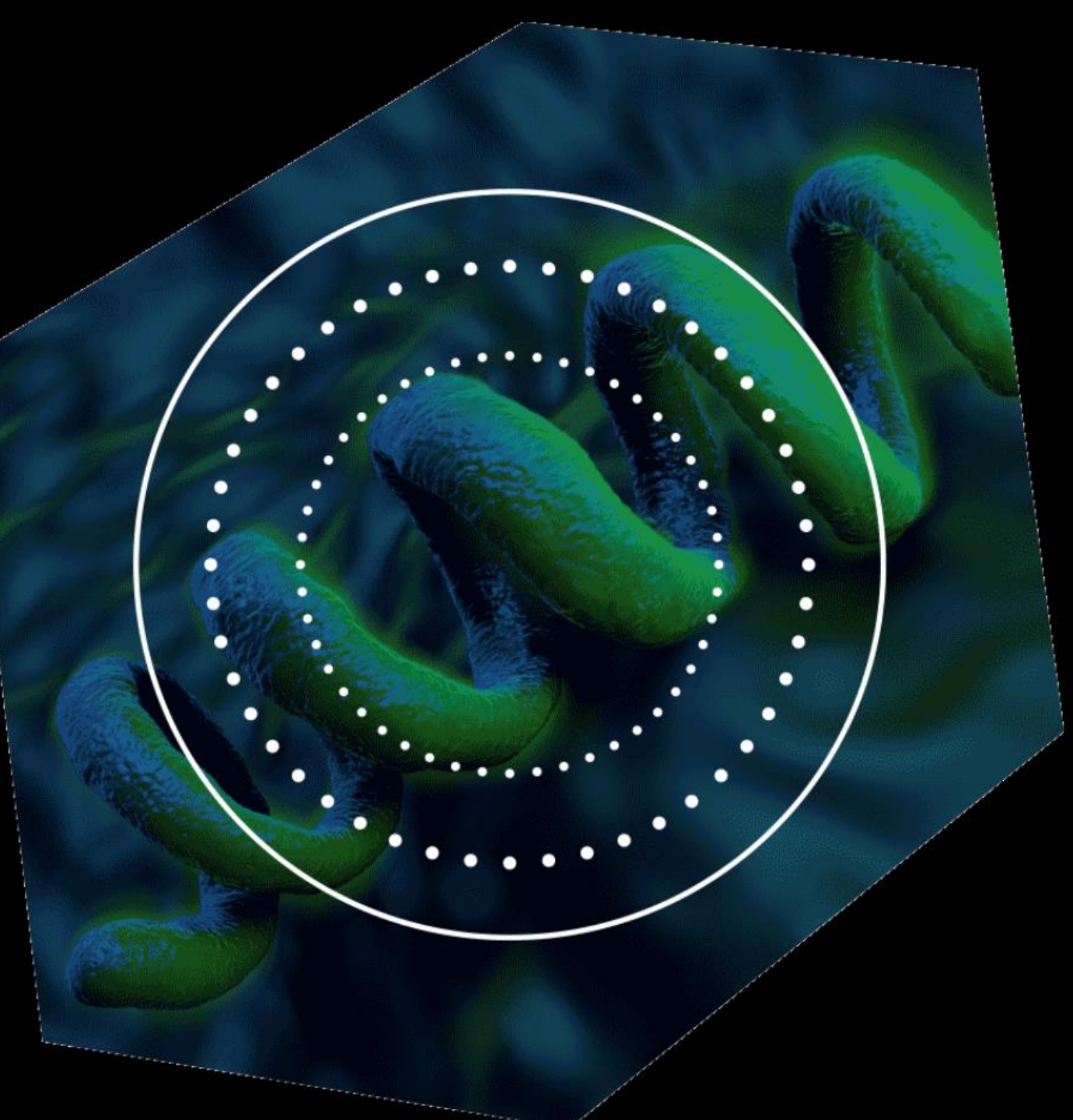

Lyme Disease: Barriers, Market Dynamics and Commercial Challenges

FLIGHTPATH
BIOSCIENCES, INC

Matt Tindall
Founder, President & CEO

(NASEM July 11th, 2024)

Background and Context

Company Overview

- Founded in 2019 to develop new therapeutics and deploy multi-omics technologies to understand early and late Lyme disease

- **Today, Flightpath Biosciences is the world's only life sciences company focused on developing new therapeutics for the treatment of Lyme disease**
  - Co-founding Scientist: Kim Lewis, PhD @ Northeastern University
  - By 2021 we had a lead drug candidate: FP-100 (hygromycin A) – the first new, narrow-spectrum antibiotic prospectively developed as a potential treatment for Lyme disease
  - Supported by all 3 Lyme disease foundations
  - Phase I clinical study began in May 2024

…but there is more to the story…

Company Overview

- Initially focused on broad-spectrum antibiotics; ***ruled them out***
- Pitched the business to 30+ angel investors, foundations and early-stage funds; **limited interest and traction**
- Licensed Hygromycin A and began initial development work; **refocused on targeted, narrow-spectrum treatments with potential to spare the gut microbiome**
- Conducted a massive clinical biomarker study; **analysis was challenging, exited diagnostics as a business area to focus on therapeutic development**
- Had hundreds of conversations with potential partners, investors, foundations, Lyme patients, Lyme families, caregivers and physicians; **developed a thesis for "how to achieve success in Lyme"**

…

- In short, we stumbled into every hurdle and roadblock in Lyme disease; **but we learned critical lessons and we are gaining momentum**

Commercial Observations (4)

- Market Opportunity for a New Lyme Disease Drug is Unclear to Investors
- Complexity of Late-Stage Disease Represents a “Superhuman Sample and Data Scale Problem”
- Question Everything About Early Stage Disease Treatment
- Need to Change the Public Narrative

Lesson #1: Traditional Venture Capital Investors Can't Value the Market

- Market size ($)
- Diagnostic uncertainty
- Guidelines are clear and recommend "what's available"; clinical practice varies widely
- Clinical endpoints ill-defined in early Lyme (until FDA issued guidance in 2023), none for late Lyme
- Heavy generic competition, pricing and reimbursement concerns

Anecdotes:

- "According to my GP colleagues, acute Lyme is not a problem"; guidelines are clear, drugs are cheap and widely available
- Repurposed small molecule drug story
- Lead drug is "too early stage, high risk, we usually get involved after phase I"
- What causes chronic Lyme?
- Does your drug treat Chronic Lyme?
- Does it treat persistent infections? Cross the BBB?
- Does your drug treat all Tick-Borne Infections?
- What else does your drug do?
- What is your "platform technology"?
- Doesn't hit our investment thesis
- etc…

Key Takeaways:

- We needed a different type of investor
- We needed to deliver a "first commercial win" to change the market dynamics.
- We needed to reduce risk for traditional VC investors

One model resonated: Cystic Fibrosis Foundation / Vertex Pharmaceuticals

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Lesson #2: Superhuman Data Scale & Analysis - Open Collaboration Required

- Molecular biology tools exist
- Artificial intelligence / ML can now be applied to ~200 historical publications and to unique data sets; but where are the scaled data sets
- Well characterized samples and funding for collection and analysis too limited
- Health system, academic and foundation silos remain a serious obstacle

- Grants: while progress has been made - difficult to win, narrow focus, increments too small, too many rules / restrictions / requirements and too time consuming for commercial enterprises to realistically pursue
- Scaled funding by corporate and VC investors does not exist

…but we have tried…

Vision: Vastly Scale-up Academic Evidence to Confirm Unique Biological Signals in CLD

Based on 4 precedent academic publications, Flightpath launched **the largest and most comprehensive clinical biomarker study of chronic Lyme disease in history to drive product development initiatives**

Objectives

Validate CLD with scientific evidence

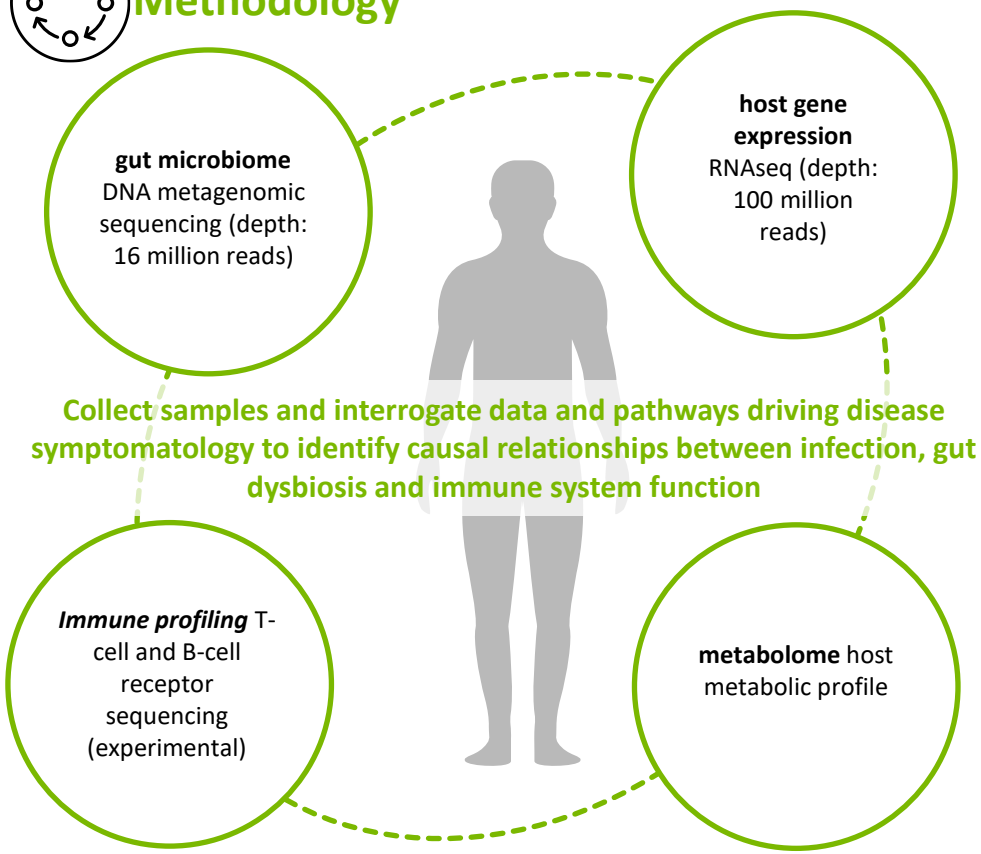
…

Develop a first-in-class **diagnostic** and a first-of-a-kind **therapeutic** for Chronic Lyme Disease

Strategy

Conduct scaled **comprehensive "omics" study** to validate previous molecular signatures in Chronic Lyme Disease patients

Methodology



Status:

Joined G.2 Class of Illumina Accelerator (March 1st 2021)

IRB approval received March 24th - **Enrollment Complete in 12 hours**

Status: 436 Lyme + and 125 Healthy samples collected – **Raw Data Analysis (7Tbs)**

PAUSED – Seeking analysis partners

Takeaway: We need a more creative version of the "X-Prize" concept to understand Lyme IACI

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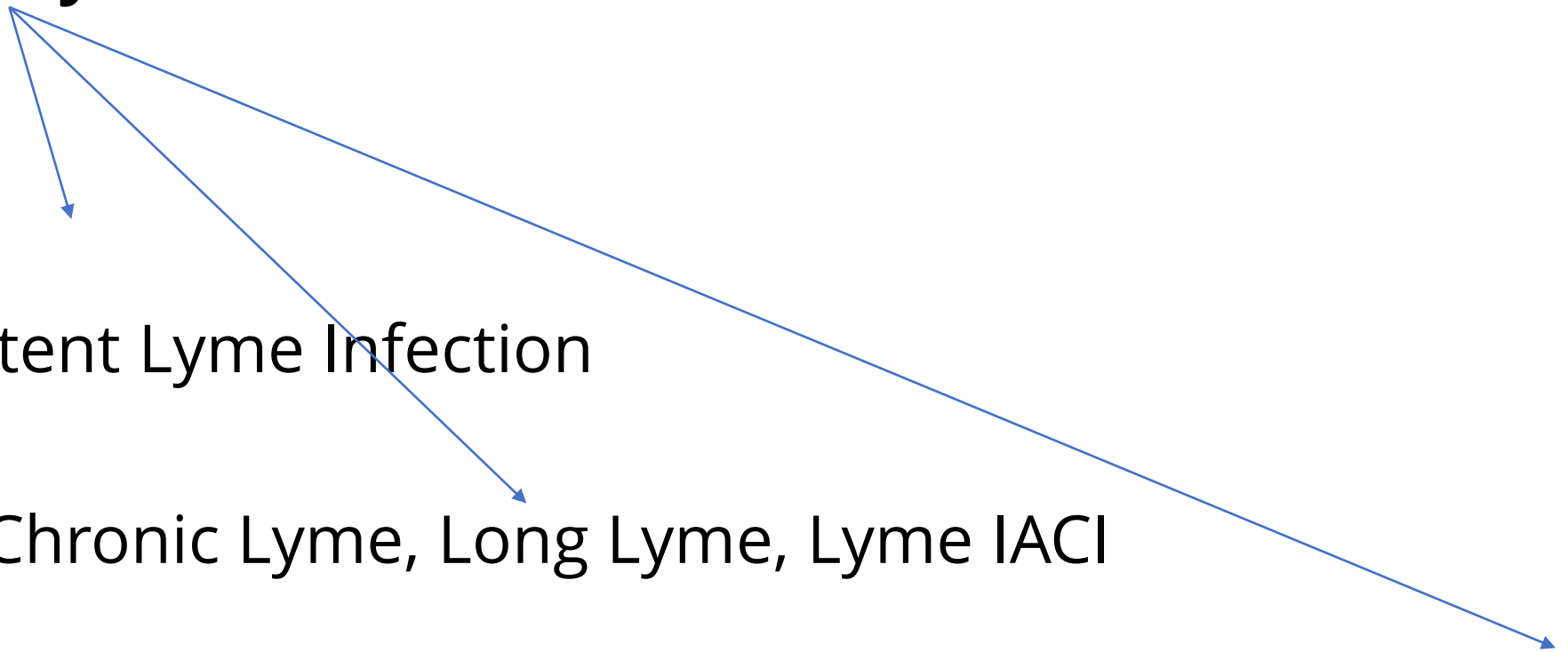
Lesson #3: Question Everything

Acute Lyme Infection



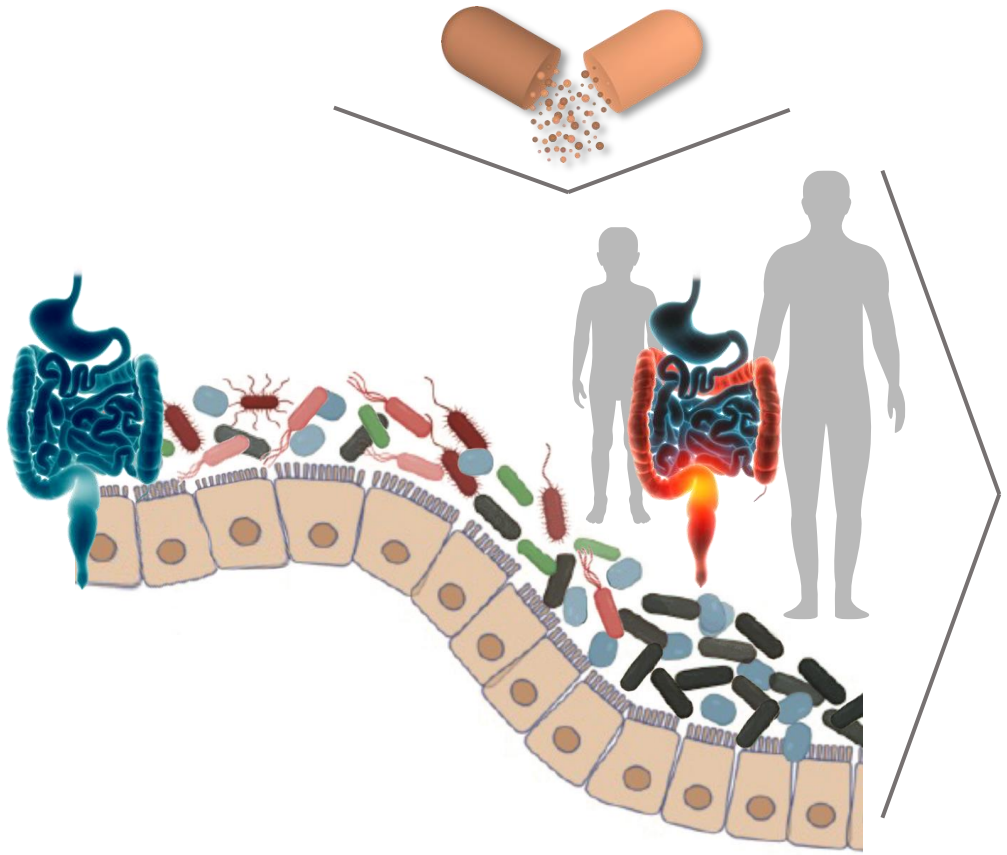
Persistent Lyme Infection

Chronic Lyme, Long Lyme, Lyme IACI

IACI (?)

Broad-Spectrum Antibiotics and the Body's Sensitive Microbiome(s)

Durable loss of gut microbiome diversity (dysbiosis) can lead to immune dysregulation, endocrine dysfunction and increased risk of chronic diseases



- **Obesity**
- **Diabetes**
- **Asthma**
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- **Depression**

loss of microbiome diversity and increased risk of chronic diseases

ARTICLE IN PRESS

MAYO CLINIC

ORIGINAL ARTICLE

Association of Infant Antibiotic Exposure With Childhood Health Outcomes

Zaira Aversa, MD, PhD; Elizabeth J. Atkinson, MS; Marissa J. Schafer, PhD; Regan N. Theiler, MD, PhD; Walter A. Rocca, MD; Martin J. Blaser, MD; and Nathan K. LeBrasseur, PhD

Abstract

Objective: To investigate the extent to which antibiotic exposure in the first 2 years of life is associated with the risk of immunological, metabolic, and neurobehavioral health conditions with childhood onset.

Patients and Methods: In this population-based cohort study, we identified all children born in Olmsted County, Minnesota, between January 1, 2003, and December 31, 2011, through the Rochester Epidemiology Project medical records-linkage system. Demographic characteristics, antibiotic prescriptions, and diagnostic codes through June 30, 2017, were retrieved using the Rochester Epidemiology Project infrastructure. Time-to-event analysis was performed to assess the impact of antibiotic exposure on the risk of several adverse health conditions.

Results: This study included 14,572 children (7026 girls and 7546 boys), of whom 70% (10,220) received at least 1 antibiotic prescription during the first 2 years of life. Early antibiotic exposure was associated with an increased risk of childhood-onset asthma, allergic rhinitis, atopic dermatitis, celiac disease, overweight, obesity, and attention deficit hyperactivity disorder (hazard ratios ranging from 1.20 to 2.89; $P<.05$ for all). The associations were influenced by the number, type, and timing of antibiotic exposure. Moreover, children exposed to antibiotics had a higher probability of having combinations of conditions, particularly when given multiple prescriptions.

Conclusion: The present study finds significant associations between early life antibiotic exposure and several distinct health conditions with childhood onset. Additional research is warranted to establish practical guidelines to optimize the benefit and minimize the risk of antibiotics in children.

 ■ Mayo Clin Proc. 2020;■(■):1-12

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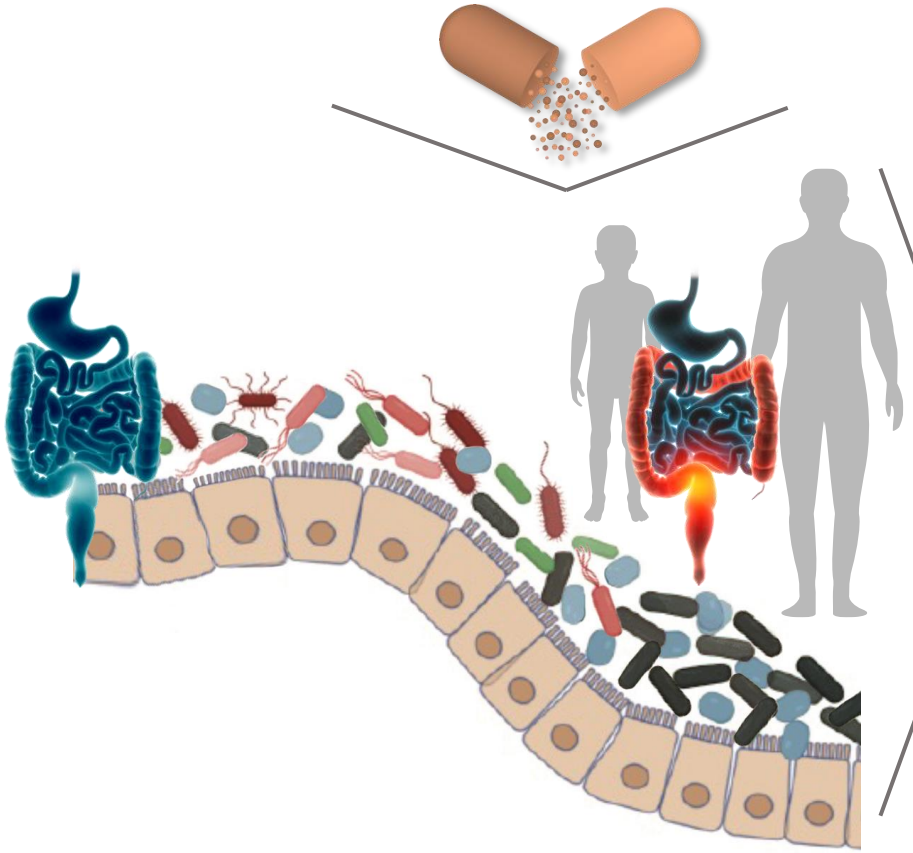

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loss of microbiome diversity and increased risk of chronic diseases

Unravelling the collateral damage of antibiotics on gut bacteria

https://doi.org/10.1038/s41586-021-03986-2
Received: 6 November 2019
Accepted: 1 September 2021
Published online: 13 October 2021
Check for updates

Lisa Maier[1,2,3,15], Camille V. Goemans[1,15], Jakob Wirbel[4], Michael Kuhn[4], Claudia Eberl[5,6], Mihaela Pruteanu[1,12], Patrick Müller[2,3], Sarela Garcia-Santamarina[1], Elisabetta Cacace[1], Boyao Zhang[4], Cordula Gekeler[2,3], Tisya Banerjee[1,13], Exene Erin Anderson[1,14], Alessio Milanese[4], Ulrike Löber[7,8], Sofia K. Forslund[4,7,8], Kiran Raosaheb Patil[4,9], Michael Zimmermann[4], Bärbel Stecher[5,6], Georg Zeller[4], Peer Bork[4,8,10,11] & Athanasios Typas[1,4]

Antibiotics are used to fight pathogens but also target commensal bacteria, disturbing the composition of gut microbiota and causing dysbiosis and disease[1]. Despite this well-known collateral damage, the activity spectrum of different antibiotic classes on gut bacteria remains poorly characterized. Here we characterize further 144 antibiotics from a previous screen of more than 1,000 drugs on 38 representative human gut microbiome species[2]. Antibiotic classes exhibited distinct inhibition spectra, including generation dependence for quinolones and phylogeny independence for β-lactams. Macrolides and tetracyclines, both prototypic bacteriostatic protein synthesis inhibitors, inhibited nearly all commensals tested but also killed several species. Killed bacteria were more readily eliminated from in vitro communities than those inhibited. This species-specific killing activity challenges the long-standing distinction between bactericidal and bacteriostatic antibiotic classes and provides a possible explanation for the strong effect of macrolides on animal[3–5] and human[6,7] gut microbiomes. To mitigate this collateral damage of macrolides and tetracyclines, we screened for drugs that specifically antagonized the antibiotic activity against abundant *Bacteroides* species but not against relevant pathogens. Such antidotes selectively protected *Bacteroides* species from erythromycin treatment in human-stool-derived communities and gnotobiotic mice. These findings illluminate the activity spectra of antibiotics in commensal bacteria and suggest strategies to circumvent their adverse effects on the gut microbiota.

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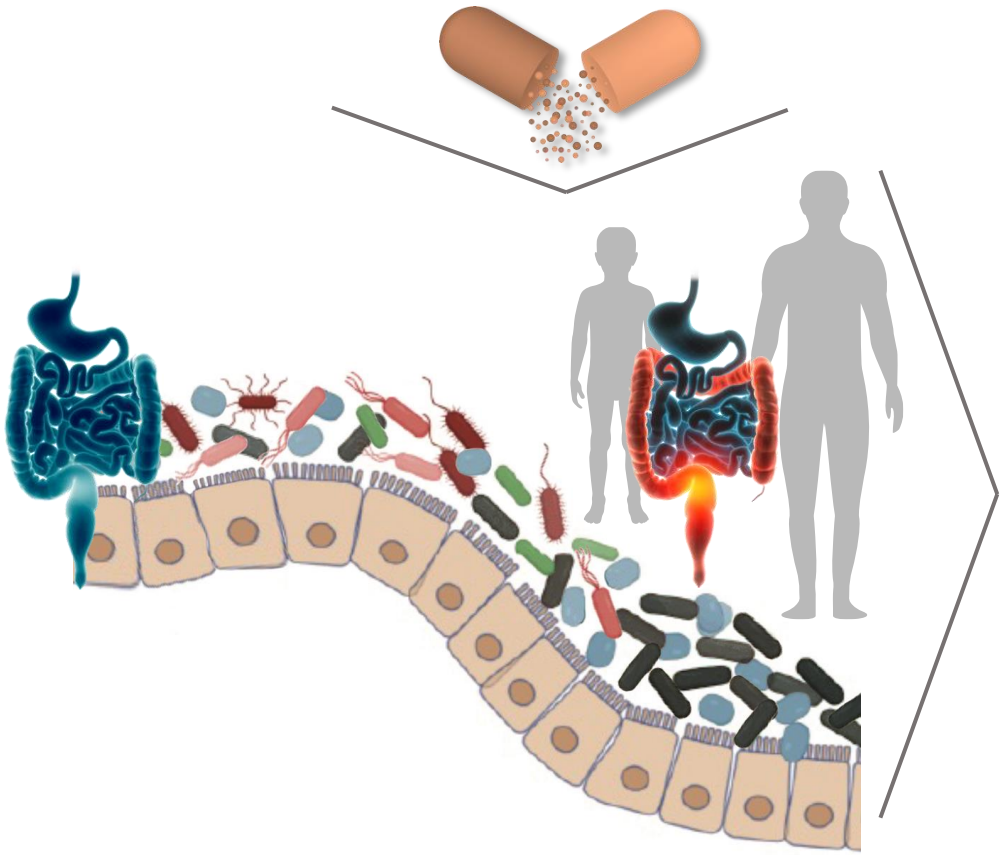

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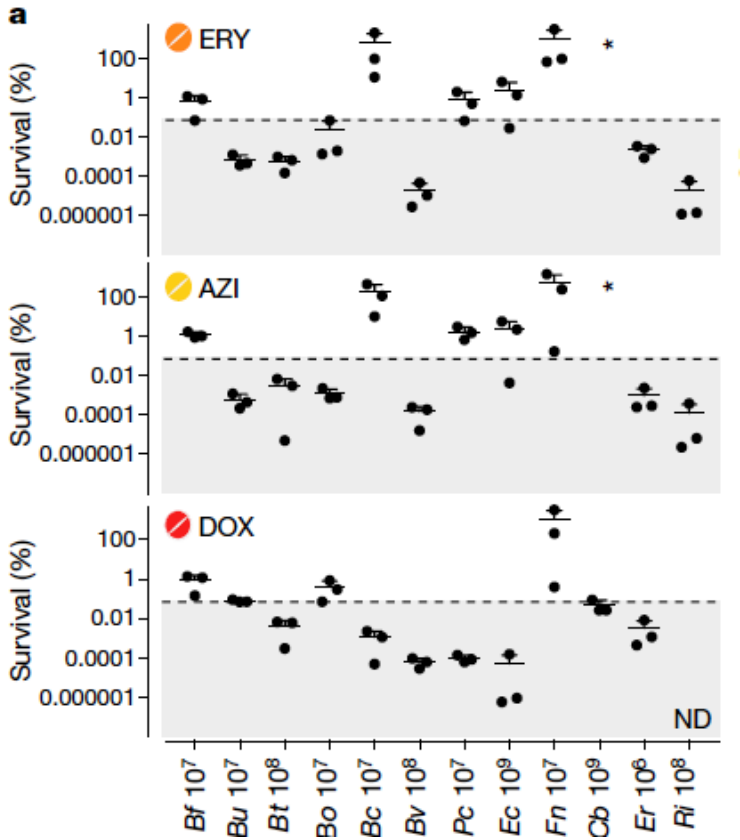

Source: Maier L et al. Unravelling the collateral damage of antibiotics on gut bacteria. Nature. 2021

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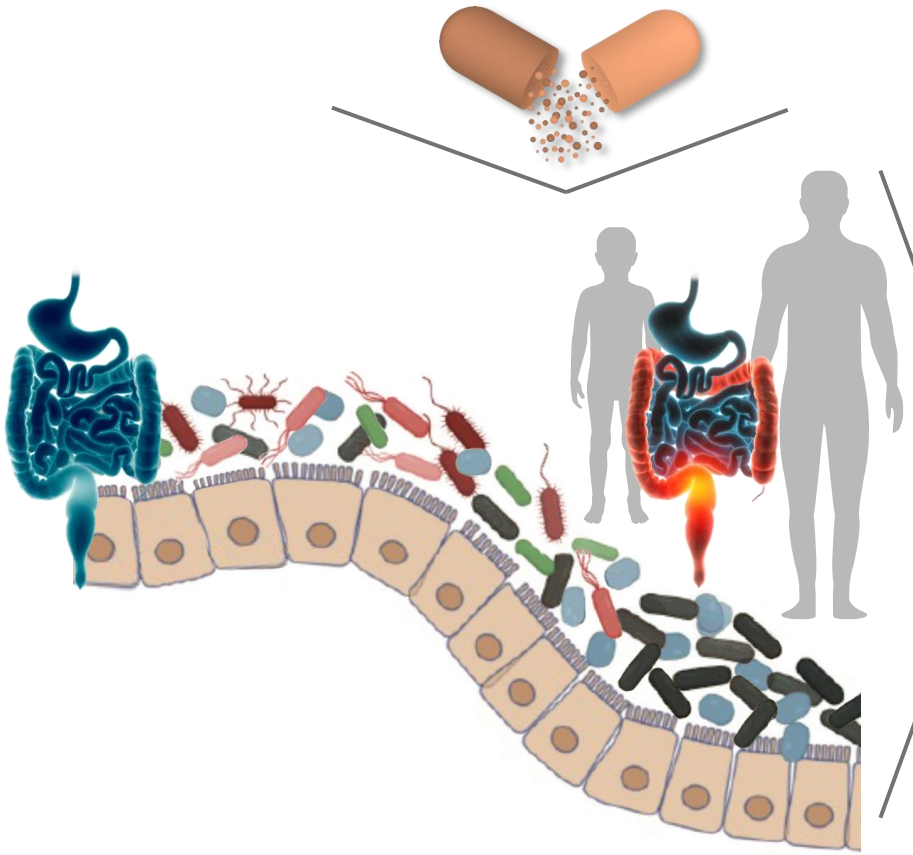

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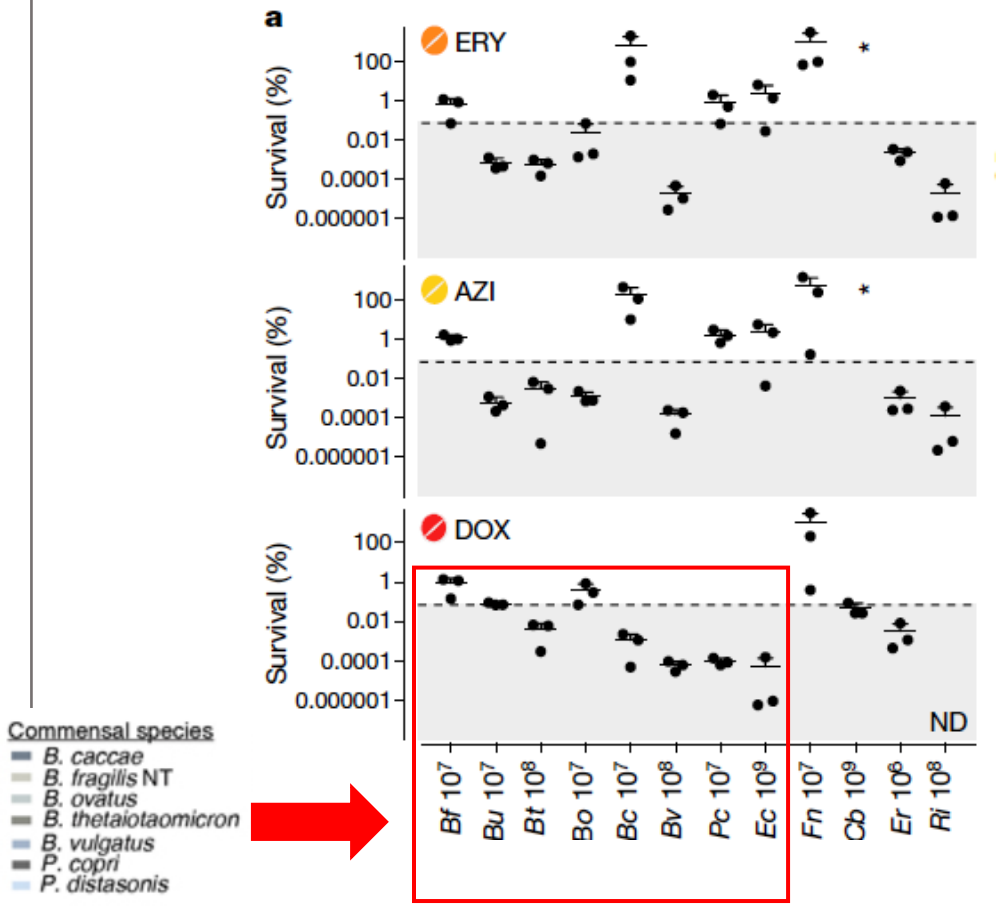

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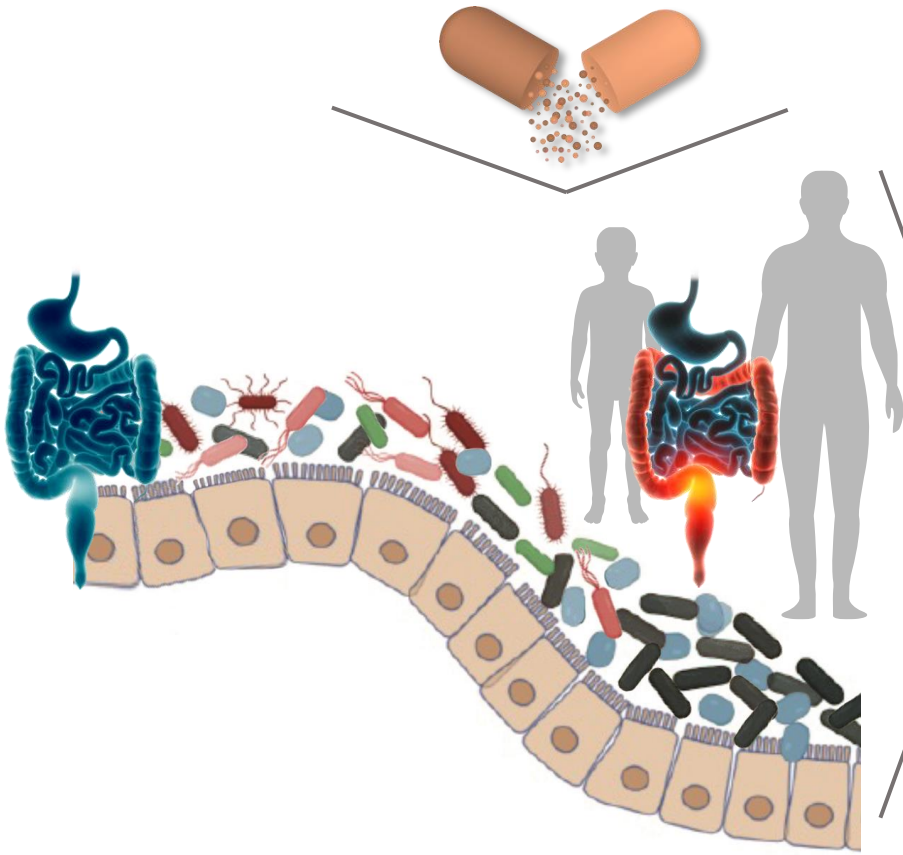

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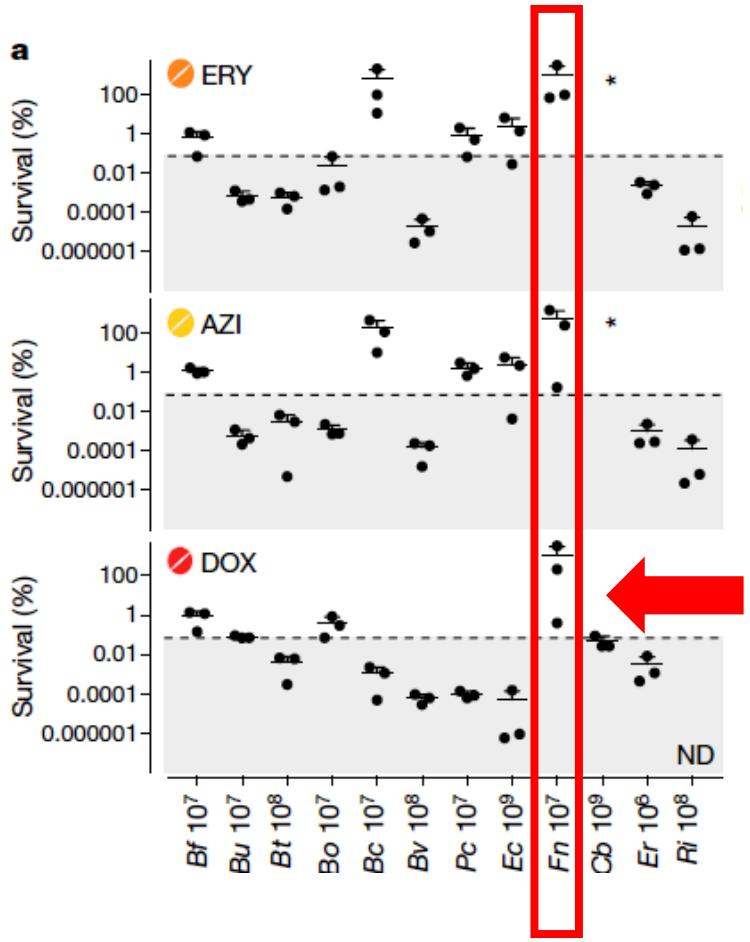

Fusobacterium nucleatum has been linked to CRC, OSCC, PD, Endometriosis, Pre-term birth, Stillbirth, Neurological disease / inflammation,

Source: Maier L et al. Unravelling the collateral damage of antibiotics on gut bacteria. Nature. 2021

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Lesson #4: Changing the Public Narrative

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Our Approach

Commercial Leadership Grounded in Strong Science and Clinical Data

Advance 1 new drug candidate for the treatment of **early Lyme disease** into human clinical development to improve the standard of care by improving near and potentially long-term outcomes

Validate the market opportunity to encourage investment by establishing a market value based on uptake, pricing and reimbursement

Repeat

Thank you


Bay Area Lyme
FOUNDATION


STEVEN & ALEXANDRA COHEN
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