Tufts Clinical and Translational Science Institute

One Health Symposium

Deborah Kochevar, DVM, PhD, DACVP

Dean and Henry and Lois Foster Professor
Cummings School of Veterinary Medicine at Tufts University

October 4, 2016

Learning Objectives

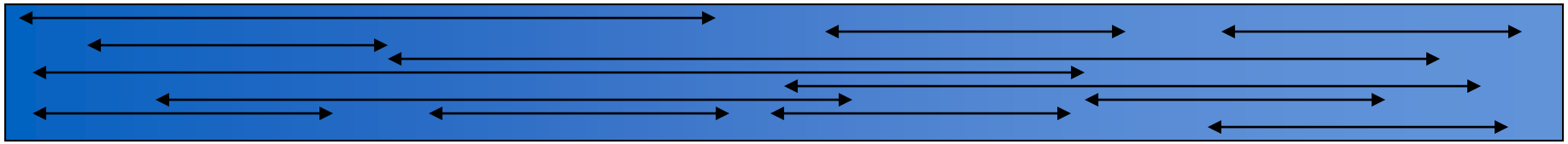
- Explain the One Health mission and research approach
- List the four One Health Priority Areas
- Discuss how One Health can support, extend, and validate translational research
- Explain the components of a successful One Health research proposal
- List the services Tufts CTSI and its One Health signature program can offer; explain how to request a One Health consultation

Tufts CTSI

Clinical and Translational Science Awards (CTSA) Program

- National Institutes of Health (NIH) program
- Launched in 2006
- A national consortium of 64 institutions
- **Mission:** to develop innovative solutions that will improve the efficiency, quality and impact of the process for turning observation in the laboratory, clinic and community into interventions that improve the health of individuals and the public

Spectrum of Clinical and Translational Research



Bench to Bedside… ↔ **...to Widespread Clinical Practice…** ↔ **…to Public Health…** ↔ **…to Health Policy**

Translation (T1) ***Translation (T2)*** ***Translation (T3)*** ***Translation (T4)***

Tufts CTSI

Tufts CTSI's Mission & Purpose

Established in 2008 to translate research into better health

- Stimulate and expedite innovative clinical and translational research, with the goal of improving the public's health
- *Entire spectrum* of clinical and translational research is critical to meeting the promise and the public's needs of biomedical science

Tufts CTSI

38 Tufts CTSI Partners

12 Tufts Schools & Centers

Cummings School of Veterinary Medicine
Fletcher School of Law & Diplomacy
Friedman School of Nutrition Science & Policy
Institute for Clinical Research & Health Policy Studies at Tufts Medical Center
Jean Mayer USDA Human Nutrition Research Center on Aging
Sackler School of Graduate Biomedical Sciences
School of Arts & Sciences
School of Dental Medicine
School of Engineering
School of Medicine
Tisch College of Citizenship & Public Service
Tufts Center for the Study of Drug Development

3 Academic Partners

Brandeis University
Northeastern University
RAND Corporation

7 Tufts-Affiliated Hospitals

Baystate Medical Center
Lahey Clinic
Maine Medical Center
New England Baptist Hospital
Newton-Wellesley Hospital
St. Elizabeth's Medical Center
Tufts Medical Center

6 Industry/Non-Profit Partners

Blue Cross Blue Shield of Massachusetts
Eli Lilly and Company
Institute for Systems Biology and P4 Medicine Institute
Minuteman Health Network
Pfizer, Inc.
Tufts Health Plan

10 Community-Based Partners

Action for Boston Community Development (ABCD)
Asian Community Development Corporation
Asian Task Force Against Domestic Violence
Asian Women for Health
Boston Chinatown Neighborhood Center
Center for Information and Study on Clinical Research Participation
Greater Boston Chinese Golden Age Center
Health Resources in Action
Museum of Science, Boston
New England Quality Care Alliance

Tufts CTSI

How Can CTSI Help?

- Connections with other researchers, industry, the community, and policy-makers across the Tufts CTSI network and national CTSA consortium via our **Navigators & Research Collaboration team**.
- Consultations on **comparative effectiveness**, **one health**, **research process improvement** and **stakeholder and community engagement** projects and grants, as well as **regulatory issues** and other areas of translation.
- Study design and data analysis (pre- and post-award) through the **Biostatistics, Epidemiology, and Research Design (BERD) Center**, including drop-in sessions.

Tufts CTSI

How Can CTSI Help?

- 24/7 clinical trial support through our **Clinical and Translational Research Center (CTRC)**.
- Informatics tools for electronic data capture (**REDCap**), resource sharing, and collaboration.
- Training & professional development including MS and PhD degrees, certificate programs, seminars & workshops, and **paid career development awards and fellowships**.
- Funding through one-year interdisciplinary **pilot studies grants** that support the initial stages of research.

Tufts CTSI

How to Request Tufts CTSI Services

- Visit www.tuftsctsi.org and submit a request

http://ilearn.tuftsctsi.org/

Live seminars are recorded for our I LEARN site.
Seminar videos can be viewed at any time, and are free!

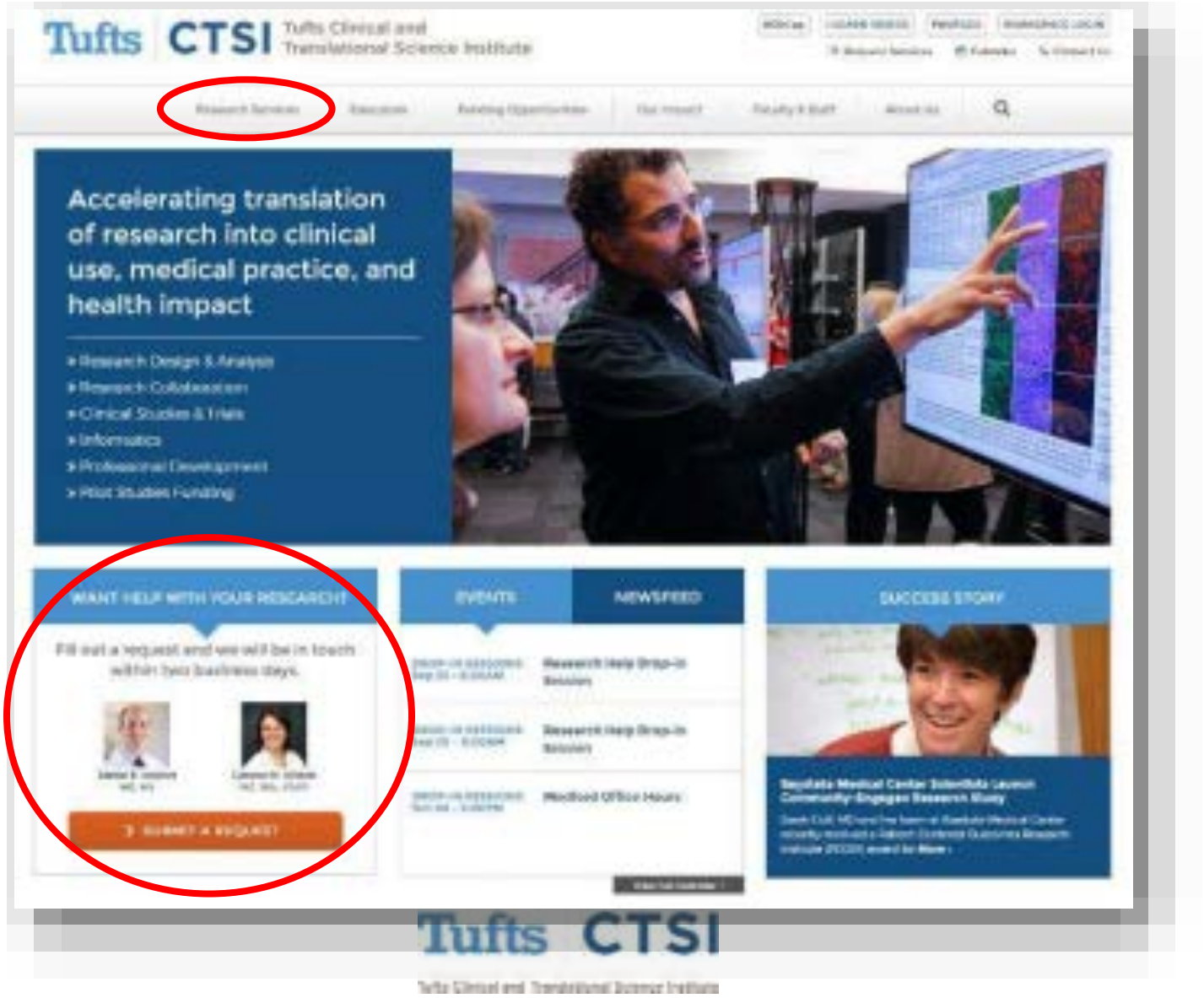
Tufts CTSI

Get Connected: CTSI Happenings

- Weekly e-newsletter with news, professional development and funding opportunities, resources, and success stories.
- Issued every Monday at 8AM
- Sign up on our website or at *http://eepurl.com/C4d9X*

Tufts CTSI

For more information: www.tuftsctsi.org



Biostatistics, Epidemiology, and Research Design Center

Norma Terrin, PhD

Director, BERD Center
Tufts CTSI

Professor of Medicine
Tufts University School of Medicine

Tufts CTSI

Biostatistics, Epidemiology, and Research Design Center

Tufts CTSI

Study Planning & Grant Application

- Free services for investigator-initiated grants and protocols:
  - Grant critique/review
  - Development of aims and hypotheses
  - Study design
  - Power and sample size calculations
  - Analysis plans
  - Randomization plans
  - Pilot data analyses for inclusion in grants

- Submit a request at www.tuftsctsi.org

Tufts CTSI

During Study or After Study Completion

- Free services:
  - Guidance on improving rejected manuscripts
- Free weekly drop-in sessions:
  - Guidance on data analyses
  - Statistical advice
  - Interpretation of results
  - Assistance with statistical software
  - Help with research process improvement
  - REDCap assistance

Tufts CTSI

During Study or After Study Completion

- Services offered for a fee:
  - Pre-analysis
    - Analysis file creation
    - Data set organization and cleaning
  - Analysis
    - Statistical analyses
    - Interpretation of results
  - Manuscript
    - Table preparation and graphics
    - Drafting statistical methods and results section
    - Manuscript review
- Submit a request at www.tuftsctsi.org

Tufts CTSI

Drop-in Sessions

- Tufts CTSI's Research Design Center/Biostatistics Research Center (RDC/BRC) offers Drop-in Sessions every Wednesday
  - 8:00 - 9:00am.
  - 35 Kneeland Street, 10th Floor Conference Room
- Drop-in Sessions are free and are staffed by Tufts CTSI epidemiologists and biostatisticians.

Tufts CTSI

Integrating Human, Animal and Environmental Health: A One Health Symposium

Tufts Clinical Translational Science Institute (CTSI)

Tuesday, October 4, 9:00AM - 1:45PM
Boston, MA

Tufts CTSI

One Health

The integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals and the shared environment. (Modified from AVMA)

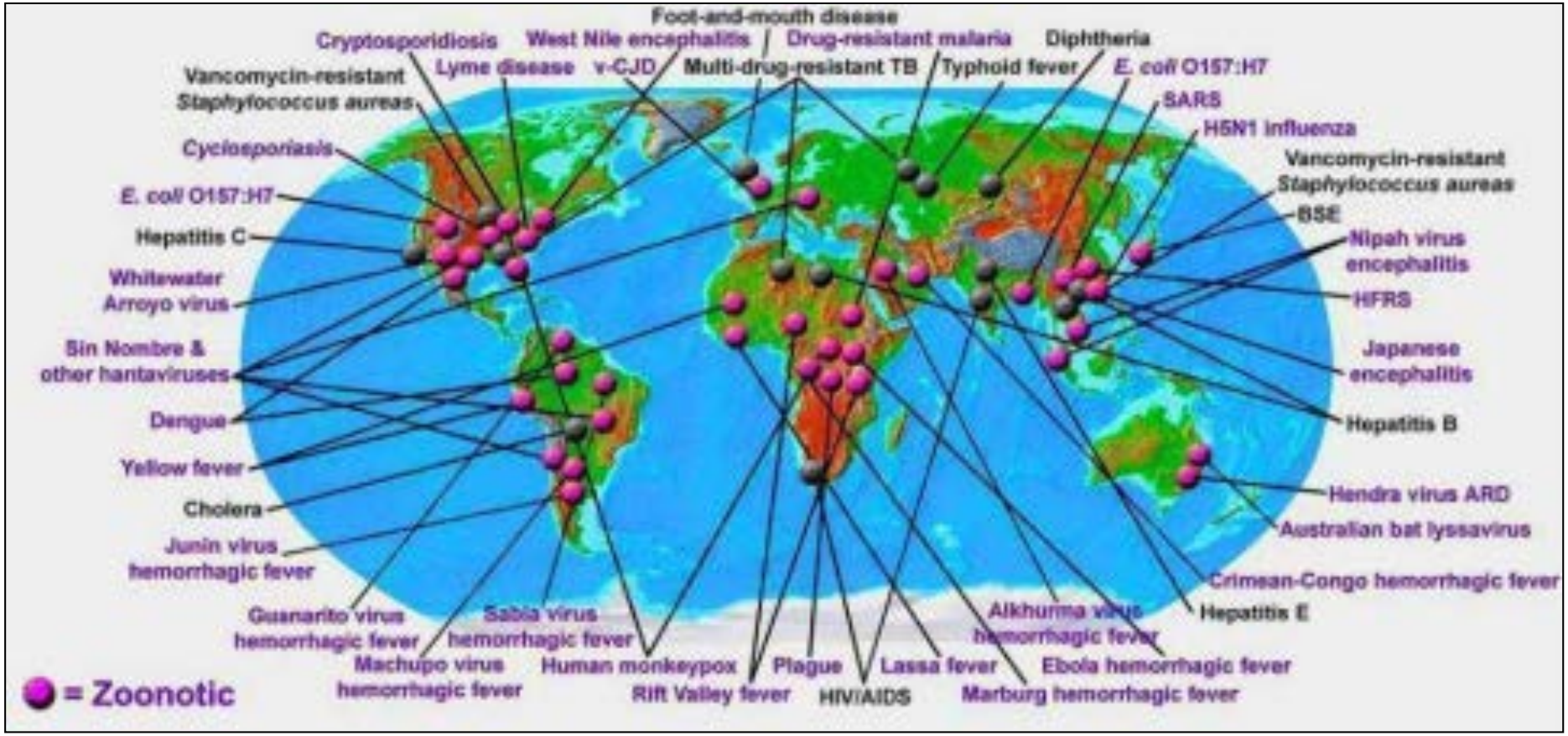
Tufts CTSI

One Health Priority Areas

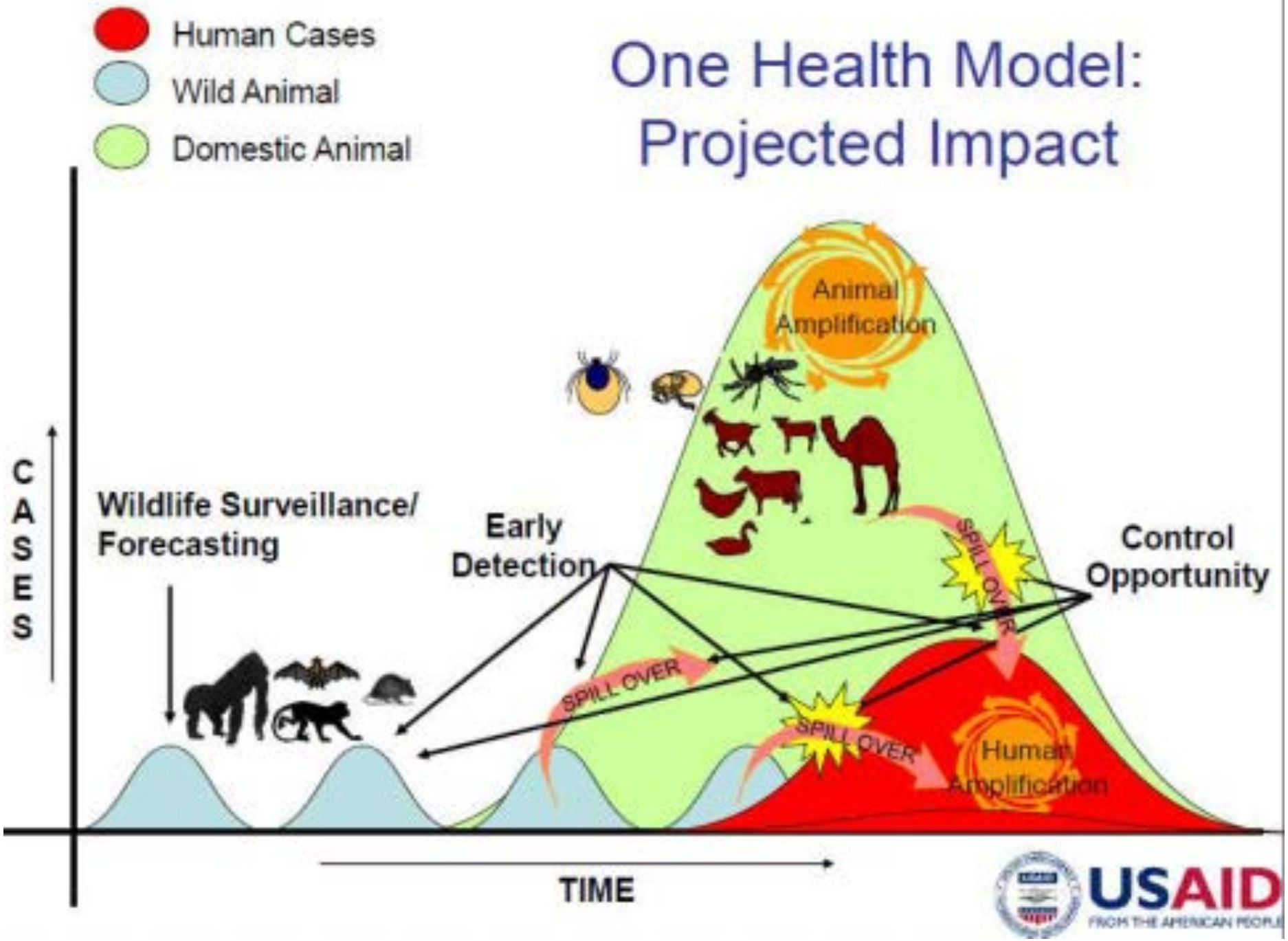
- Zoonotic infectious disease
- Naturally-occurring animal diseases
- Human-animal interactions
- Ecosystem health

Tufts CTSI

Infectious and Zoonotic Disease



Tufts CTSI


Human Cases
Wild Animal
Domestic Animal
One Health Model:
Projected Impact
Animal Amplification
Wildlife Surveillance/
Forecasting
Early
Detection
SPILL OVER
SPILL OVER
SPILL OVER
Control
Opportunity
Human Amplification
CASES
TIME
USAID
FROM THE AMERICAN PEOPLE

Ecosystem Health

Human-Animal Interactions

Tufts Institute for Human-Animal Interaction

From seeing-eye dogs to therapeutic horseback riding to therapy dogs that help children struggling with reading, the healing power of animals enriches our lives in many ways. Human Animal Interaction (HAI) goes well beyond the strong emotional bonds that people have with our pets to include all aspects of these complex, complementary relationships. While there is a great deal of enthusiasm around HAI, such as the increasing popularity of animal-assisted therapy, the science of the field is still growing.

Mission Statement

Our mission is to promote the health, strengths, and well-being of humans and animals through transdisciplinary partnerships that foster innovative research, education, and service programs in human-animal interaction.

Vision Statement

To enhance the lives of humans and animals through mutually beneficial interactions.

How to Get Involved

Sign Up for Updates

If you are either currently involved in HAI-related activities, or wish to become involved, please click here to sign up for updates about the Tufts Institute for Human-Animal Interaction. » sign up now

Paws for People

Find out more about Tufts Paws for People, our

About Us

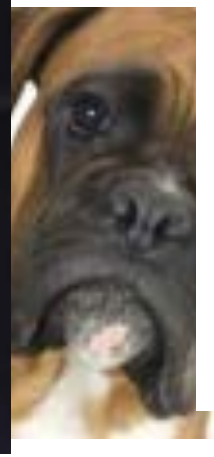
Board of Advisors

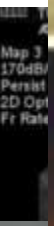
» Director: Lisa Freeman, DVM, PhD, Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine; Friedman School of Nutrition Science and Policy; and Jonathan M. Tisch College of Citizenship and Public Service, and Tufts Clinical and Translational Science Institute

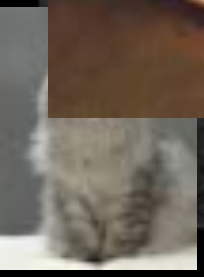
» Associate Director: Deborah Linder, DVM, Research Assistant Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine and Jonathan M. Tisch College of Citizenship and Public Service

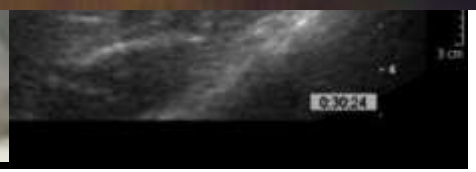
» Associate Director: Megan Mueller, PhD, Research Assistant Professor, Department of Clinical Sciences and Center for Animals and

Natural animal models









Tufts CTSI

Tufts UNIVERSITY | Tufts Human-Animal Cancer Collaborative

HOME | ABOUT | IN THE NEWS | PUBLICATIONS | UNDERWAY NOW

http://cancercollaborative.tufts.edu

Tufts Human-Animal Cancer Collaborative

Cancer does not discriminate –it is the number one cause of death in adult dogs and has become as common in cats as in humans. In fact, dogs and cats develop cancers that resemble the human disease and often experience a similar response to therapy. Cancer care for dogs and cats provides an opportunity for comparative oncology studies that may foster discovery and clinical translation that is relevant to humans as well as animals.

Human and veterinary oncologists are aligned in their pursuit of scientific discovery to find better outcomes and increase survival rates for their patients regardless of species – human, dog or cat.

Physicians, researchers and veterinarians who comprise Tufts Human-Animal Cancer Collaborative share a passion to revolutionize cancer care for humans and companion animals. They build collaborative bridges across Tufts health science campuses, share knowledge and partner on research to help uncover unique cancer biology, advance cancer treatments and improve patient care.

Mission:

Tufts Human-Animal Cancer Collaborative strives to advance mechanistic understanding of cancers leading to improved outcomes in humans and animals.

Partners in Healing

Veterinarians and physicians are poised to deliver a knockout blow to the cancers their patients share. Read more...

Partners in Healing

Work being done at Tufts is helping to advance the field of comparative oncology, which looks at how cancer behaves and is best treated in people and other species. Video: Stefan Hacker – See more on Tufts Now

Member of the Tufts Human-Animal Cancer Collaborative

Shelkot Anwer, DMVH, PhD, Professor and Associate Dean, Department of Bio Medical Sciences, Cummings School of Veterinary Medicine

Lisa Barber, DVM, DACVIM, Assistant Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine

John Berg, DVM, MS, DACVS, Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine

Kristine Burgess, DVM, MLA, DACVIM, Assistant Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine

Andrew Evans, D.O., M.Sc., Professor, Tufts University School of Medicine

Michele Kryvoliber, Assistant Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine

Nick Frank, DVM, PhD, DACVIM, Professor & Department Chair, Department of Clinical Sciences, Cummings School of Veterinary Medicine

Caitlin Hinton, MS, VMD, DACVR, Assistant Professor, Department of Clinical Sciences, Cummings School of Veterinary Medicine

Philip Hinds, PhD, Professor & Chair, Department of Developmental, Molecular & Chemical Biology, Tufts University School of Medicine

Sara Jennings, Assistant Professor, Department of Bio Medical

Tufts CTSI One Health

- CTSI One Health Committee
- Tufts student One Health clubs
- CTSI One Health Alliance (COHA)

Tufts CTSI

One Health Symposium

Project Presentations

Tufts CTSI

A Safe, Inexpensive, Easily Administered enterohemorrhagic *E. coli* Vaccine for Cattle

John Leong, MD, PhD
Linc Sonenshein, PhD
Saul Tzipori, DVM, PhD, DSc, FRCVS

Tufts University School of Medicine
Tufts University Cummings School of Veterinary Medicine

Attaching and Effacing (AE) Pathogens

- **Enterohemorrhagic *E. coli* (EHEC)**

Attaching and effacing lesion

Tufts CTSI

Attaching and Effacing (AE) Pathogens

- **Enterohemorrhagic E. coli (EHEC)**
  - **~100,000 cases annually**
  - **Encodes Shiga toxin on a lambdoid phage (ΦStx)**
    - Hemorrhagic colitis
    - 5-10% -> hemolytic uremic syndrome (HUS)
    - Antibiotic Rx -> increased Shiga toxin

Attaching and effacing lesion

Tufts CTSI

Attaching and Effacing (AE) Pathogens

- **Enterohemorrhagic E. coli (EHEC)**
  - **~100,000 cases annually**
  - **Encodes Shiga toxin on a lambdoid phage (ΦStx)**
    - Hemorrhagic colitis
    - 5-10% -> hemolytic uremic syndrome (HUS)
    - Antibiotic Rx -> increased Shiga toxin
- **Citrobacter rodentium**
  - **Efficiently colonizes conventional mice.**
  - **Lacks ΦStx and does not produce Shiga toxin.**
  - **Non-hemorrhagic colitis**

Attaching and effacing lesion

Tufts CTSI

Attaching and Effacing (AE) Pathogens

- **Enterohemorrhagic E. coli (EHEC)**
  - **~100,000 cases annually**
  - **Encodes Shiga toxin on a lambdoid phage (ΦStx)**
    - Hemorrhagic colitis
    - 5-10% -> hemolytic uremic syndrome (HUS)
    - Antibiotic Rx -> increased Shiga toxin
- **Citrobacter rodentium**
  - **Efficiently colonizes conventional mice.**
  - **Lacks ΦStx and does not produce Shiga toxin.**
  - **Non-hemorrhagic colitis**

Attaching and effacing lesion

Tufts CTSI

Attaching and Effacing (AE) Pathogens

- **Enterohemorrhagic E. coli (EHEC)**
  - **~100,000 cases annually**
  - **Encodes Shiga toxin on a lambdoid phage (ΦStx)**
    - Hemorrhagic colitis
    - 5-10% -> hemolytic uremic syndrome (HUS)
    - Antibiotic Rx -> increased Shiga toxin
- **Citrobacter rodentium**
  - **Efficiently colonizes conventional mice.**
  - **Lacks ΦStx and does not produce Shiga toxin.**
  - **Non-hemorrhagic colitis**

Attaching and effacing lesion

Tufts CTSI

Cattle are major source of EHEC

Tufts CTSI

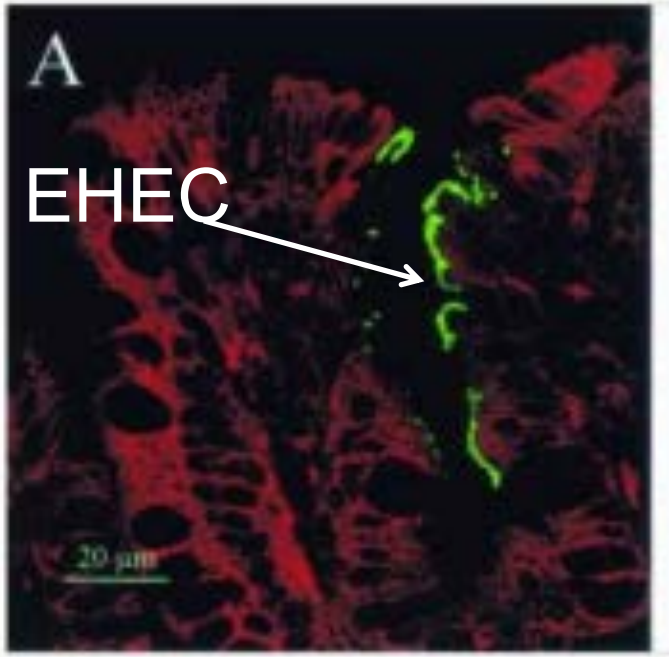
Cattle are major source of EHEC

- EHEC colonization of mucosal surface at anorectal junction

Tufts CTSI

Cattle are major source of EHEC

- EHEC colonization of mucosal surface at anorectal junction



Stuart Naylor, David Gally

Tufts CTSI

Cattle are major source of EHEC

- EHEC colonization of mucosal surface at anorectal junction

Tufts CTSI

Tufts CTSI

Tufts Clinical and Translational Science Institute

Economic cost of EHEC

- 2007: Topps Meat, a $31 million company, out of business after it recalled 21.7 million pounds of frozen hamburgers.

- 2015: an EHEC outbreak associated with Chipotle Mexican Grill resulted in cases in 11 states.

Tufts CTSI

Potential vaccination strategy

- Gally: Three antigens, when used as an intramuscular vaccine cocktail, resulted in 1000-fold decrease in EHEC fecal shedding.
  - Tir
  - Intimin
  - EspA

Potential vaccination strategy

- Gally: Three antigens, when used as an intramuscular vaccine cocktail, resulted in 1000-fold decrease in EHEC fecal shedding.
  - Tir
  - Intimin
  - EspA

Each is required for attaching and effacing lesions

Tufts CTSI

Potential vaccination strategy

- Gally: Three antigens, when used as an intramuscular vaccine cocktail, resulted in 1000-fold decrease in EHEC fecal shedding.
  - Tir
  - Intimin
  - EspA

Each is required for attaching and effacing lesions

However, too expensive to be deemed practical.

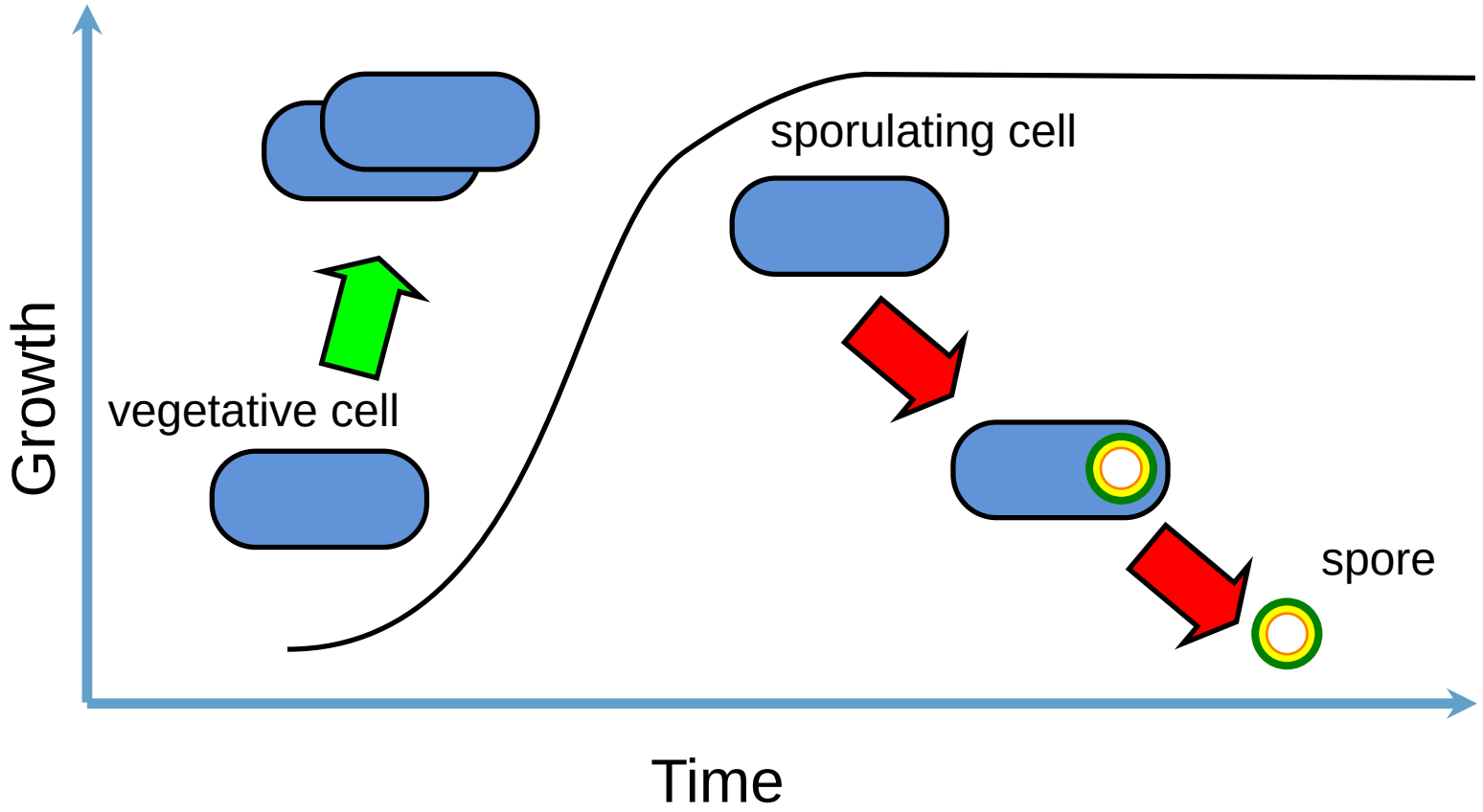
Tufts CTSI

Bacillus subtilis as a Heat-Stable, Needle-Free Vaccine Delivery System

Linc Sonenshein, PhD
Saul Tzipori, DVM, PhD, DSc, FRCVS

Tufts University School of Medicine
Tufts University Cummings School of Veterinary Medicine

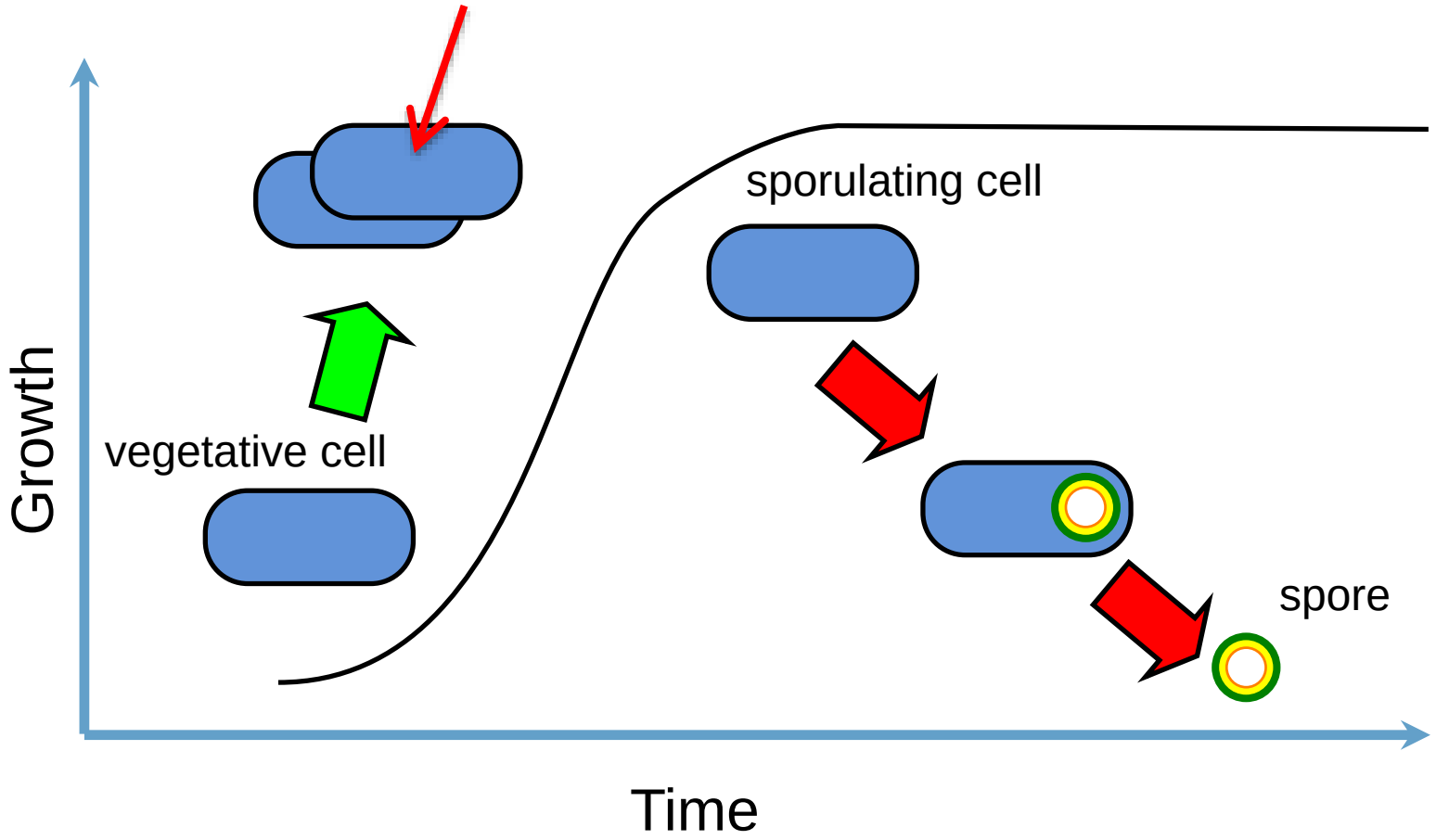
Bacillus subtilis and sporulation



Tufts CTSI

Bacillus subtilis and sporulation

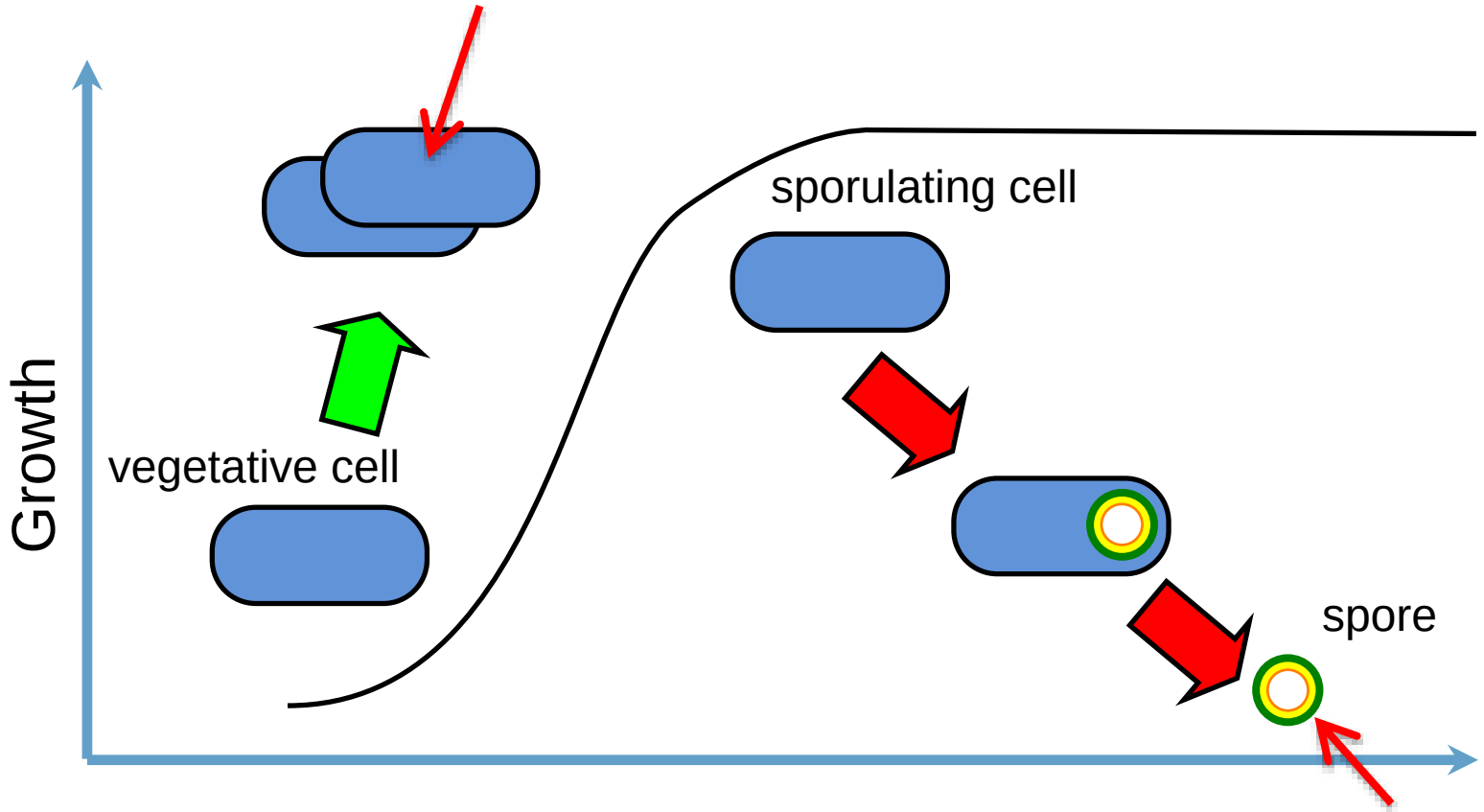
1. Produce antigens in vegetative cells



Tufts CTSI

Bacillus subtilis and sporulation

1. Produce antigens in vegetative cells

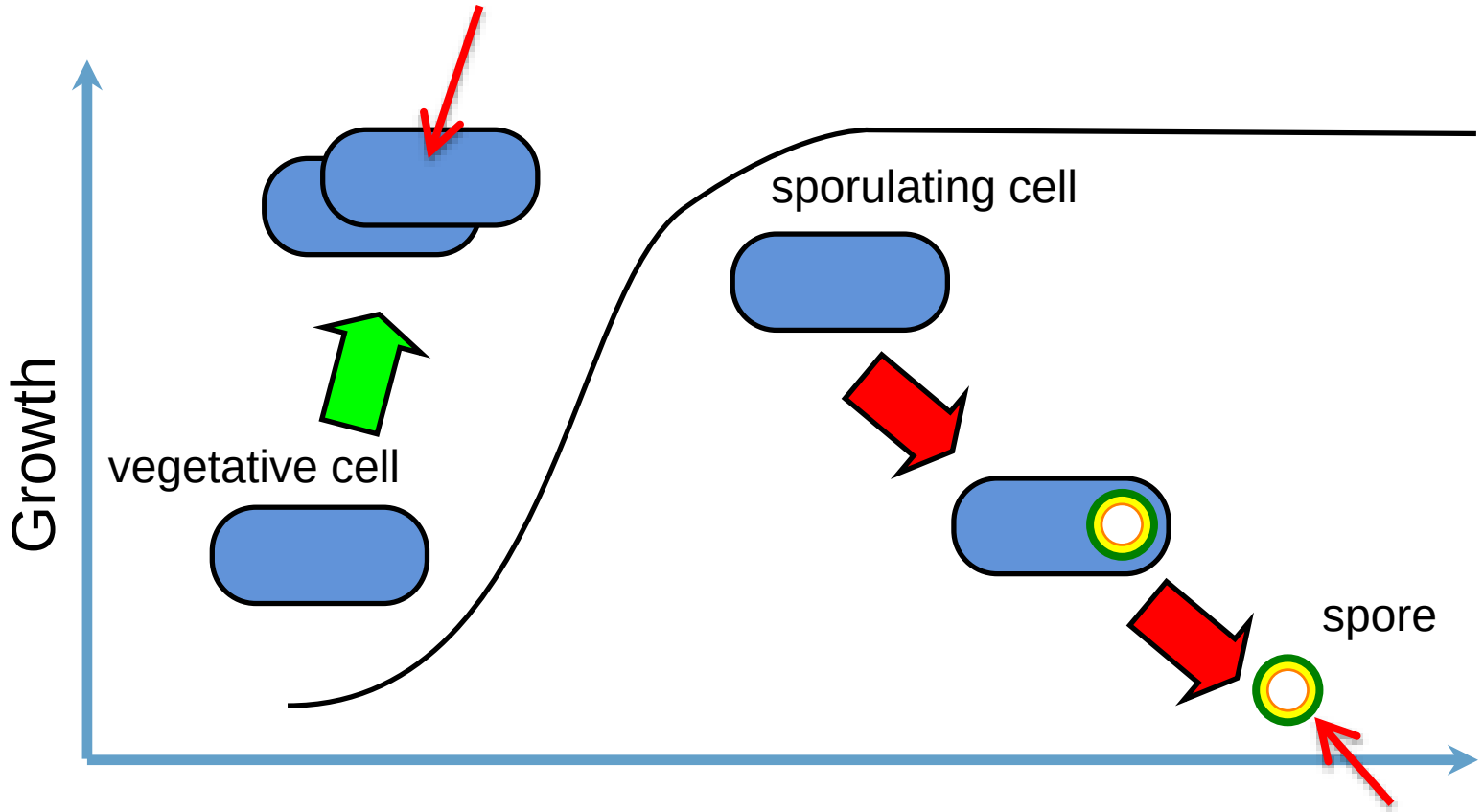


2. Produce antigens on the surface of spores

Tufts CTSI

Bacillus subtilis and sporulation

1. Produce antigens in vegetative cells



2. Produce antigens on the surface of spores

Cost: approximately $0.09 to $0.22 per dose

Test case

- Two prototype tetanus vaccine strains expressing the TetC antigen as
  - A fusion protein on the spore surface
  - In the vegetative cell cytoplasm

Tufts CTSI

Mucosal delivery of B. subtilis vaccines

- In mice and piglets, intranasal administration of TetC-expressing *B. subtilis* induces a systemic protective immune response, both Th1 and Th2.

- Both vaccines are stable at 45^{o}C for > 17 months.

Tufts CTSI

Mucosal delivery of B. subtilis vaccines

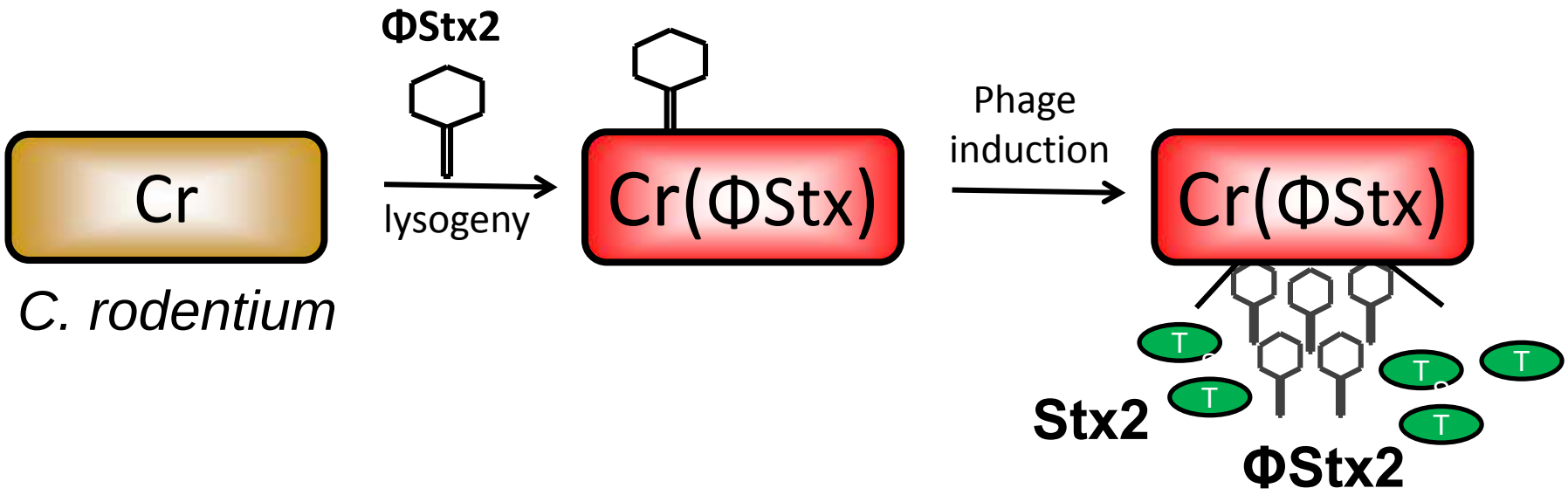
- In mice and piglets, intranasal administration of TetC-expressing *B. subtilis* induces a systemic protective immune response, both Th1 and Th2.
- Both vaccines are stable at 45^{o}C for > 17 months.
- *B. subtilis* Rota virus vaccine also efficacious in animal model.

Tufts CTSI

Challenge: EHEC does not efficiently colonize conventional mice

- Germ-free or streptomycin-treated mice have been used for EHEC infection, but well documented colonization factors are not required in these models.

Cr(ΦStx), a murine model for EHEC

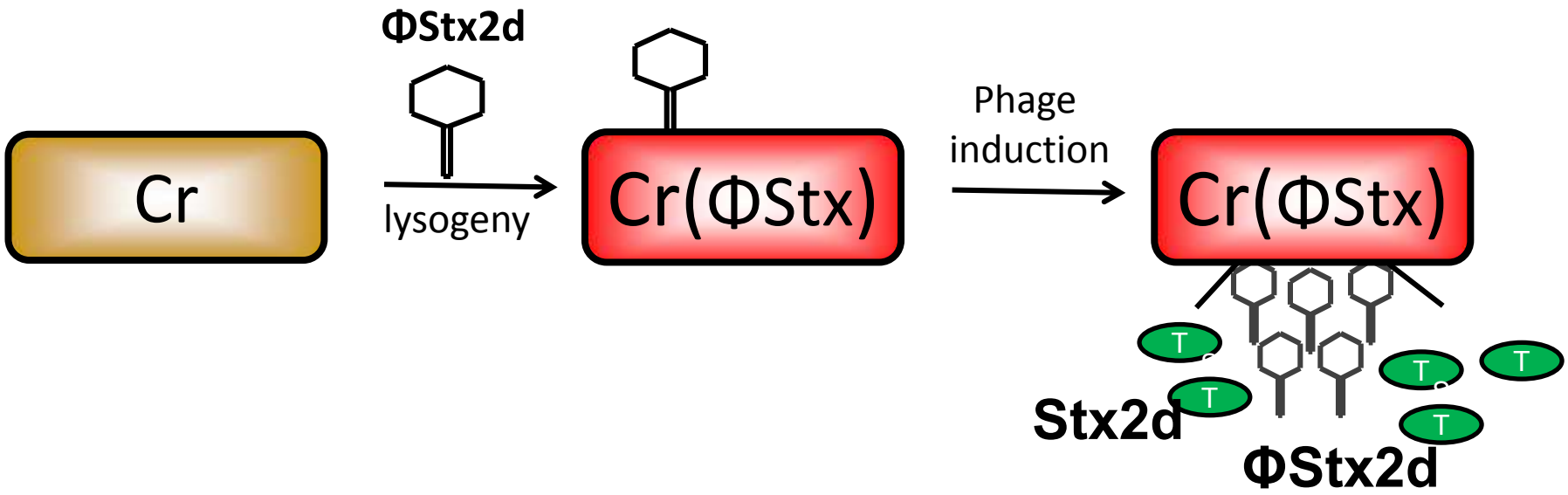


C. rodentium

Joan Butterton David Schauer

Tufts CTSI

Cr(ΦStx), a murine model for EHEC

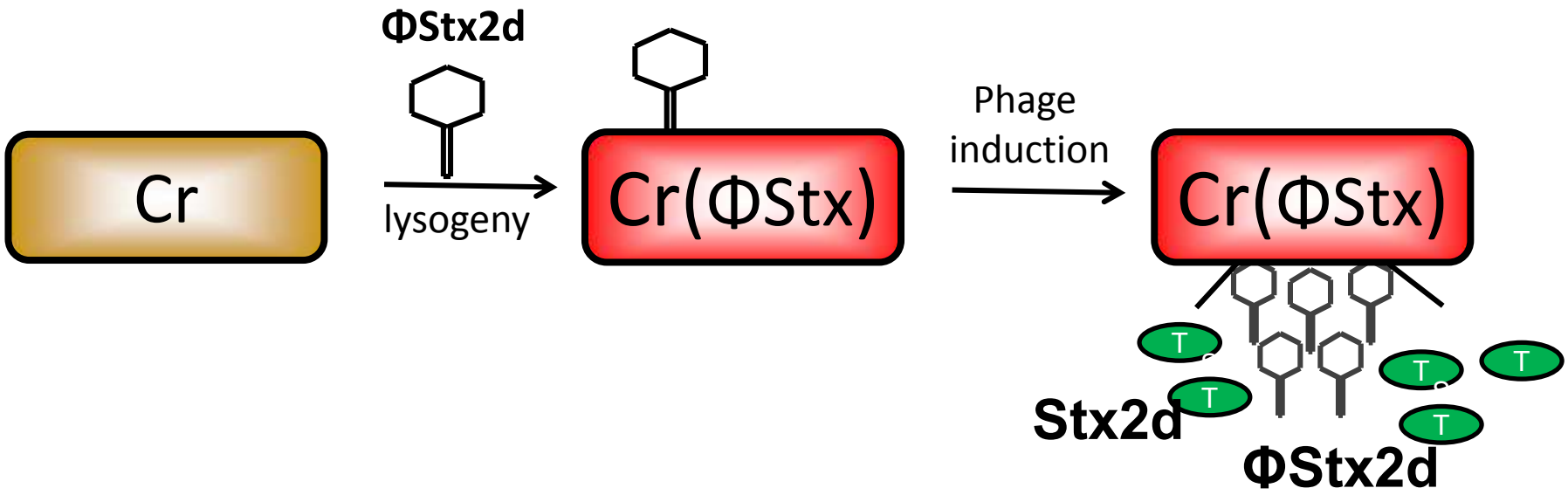


- Colonizes conventional mice, forms AE lesions on intestinal epithelium, causes lethal disease with renal manifestations.

Joan Butterton David Schauer

Tufts CTSI

Cr(ΦStx), a murine model for EHEC



Joan Butterton David Schauer

- Colonizes conventional mice, forms AE lesions on intestinal epithelium, causes lethal disease with renal manifestations.
- Colonization and disease require Tir, intimin and EspA.

Tufts CTSI

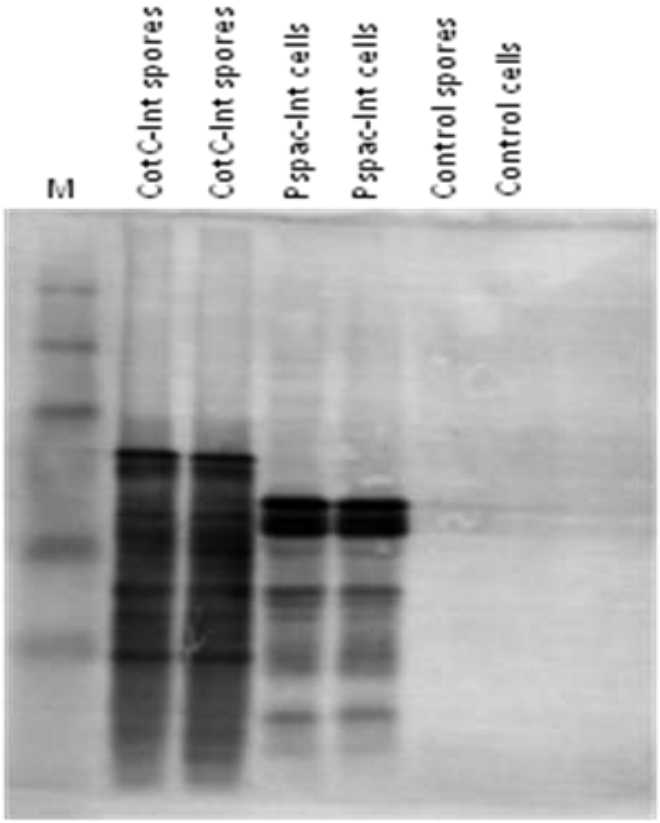
Aim 1: Generate B. subtilis vaccine strains that produce Tir, intimin or EspA.

- Several promoters and fusion partners will be tested and compared.

Tufts CTSI

Aim 1: Generate B. subtilis vaccine strains that produce Tir, intimin or EspA.

- Several promoters and fusion partners will be tested and compared.



Immunoblot of *B. subtilis* spore or cell extracts expressing EHEC intimin-531 on the spore surface or in the cell cytoplasm.

Tufts CTSI

Aim 1: Generate B. subtilis vaccine strains that produce Tir, intimin or EspA.

- Several promoters and fusion partners will be tested and compared
  - Utilize alleles from the four EHEC serotypes that comprise the major outbreaks, as well as from *C. rodentium* for proof-of-principle test in mice (see below).

Tufts CTSI

Aim 2: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in mice.

- Using IN route, test *B. subtilis* strains with a panel of adjuvants for the ability to induce a robust, long-lived immune serum and fecal IgG and IgA responses.

Tufts CTSI

Aim 2: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in mice.

- Using IN route, test *B. subtilis* strains with a panel of adjuvants for the ability to induce a robust, long-lived immune serum and fecal IgG and IgA responses.
- Test for protection from Cr(ΦStx) after immunization with mixture of *B. subtilis* harboring alleles specific to *C. rodentium*.

Aim 2: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in mice.

- Using IN route, test *B. subtilis* strains with a panel of adjuvants for the ability to induce a robust, long-lived immune serum and fecal IgG and IgA responses.
- Test for protection from Cr(ΦStx) after immunization with mixture of *B. subtilis* harboring alleles specific to *C. rodentium*.
- Test also for decolonization of mice pre-inoculated with *C. rodentium*.

Tufts CTSI

Aim 3: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in 3 m-old cattle.

- Establish the optimal dose, adjuvant, and number of immunizations for robust, long-lasting (≥6 months) mucosal and systemic antibody production.

Tufts CTSI

Aim 3: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in 3 m-old cattle.

- Establish the optimal dose, adjuvant, and number of immunizations for robust, long-lasting (≥6 months) mucosal and systemic antibody production.
- Test efficacy prior to EHEC challenge (i.e., protection).

Aim 3: Test B. subtilis Tir, intimin, and EspA vaccine strains for protection in 3 m-old cattle.

- Establish the optimal dose, adjuvant, and number of immunizations for robust, long-lasting (≥6 months) mucosal and systemic antibody production.
- Test efficacy prior to EHEC challenge (i.e., protection).
- Test efficacy following EHEC challenge (i.e., decolonization).

Tufts CTSI

Thank You

Tufts CTSI

Discussants

Caroline Genco, PhD

Deborah Linder, DVM, DACVN

Paola Massari, BS/MSc, PhD

Robin Ruthazer, MPH

Tufts CTSI

Questions?

Tufts CTSI

A One-Health Approach to Asthma Therapy: Decreasing Airway Smooth Muscle Mass Using Naturally Occurring Models of Disease in the Horse and Cat

Melissa R. Mazan, DVM, DACVIM
Heber Nielsen, MD
Daniela Bedenice, DVM, DACVIM, DACVECC
Elizabeth Rozanski DVM, DACVIM, DACVECC
Alisha Gruntman, DVM

Tufts University School of Medicine
Tufts University Cummings School of Veterinary Medicine

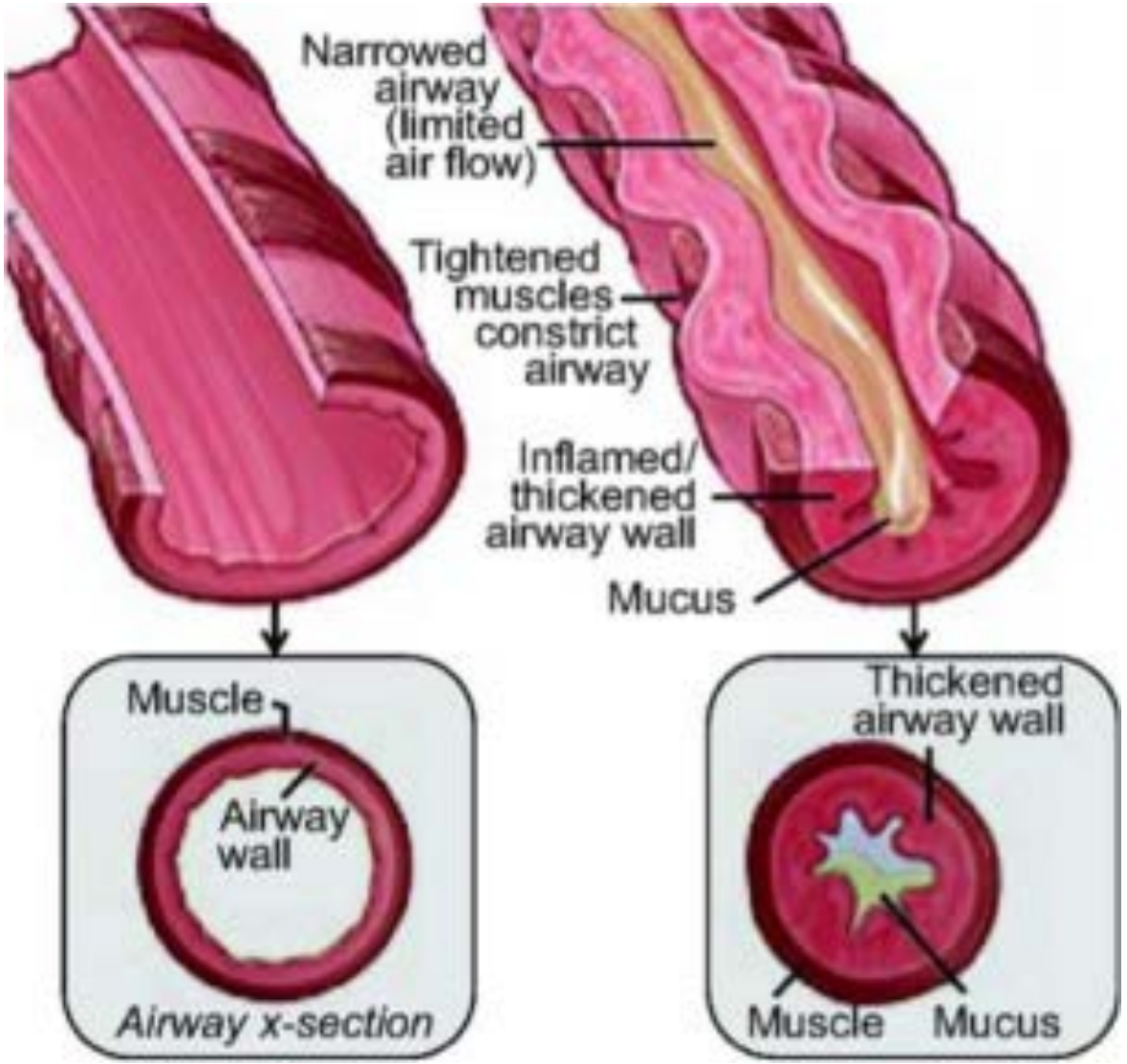
Asthma

- Afflicts 25 million in U.S., including 10 million children
- Leading cause of missed school days, ER visits, and hospitalizations
- 5,000 deaths per year in U.S., mostly children
- Current treatments only target inflammation
- 5-10% of asthma is poorly controlled with current therapies
- Severe asthmatics who are well-controlled still have significant loss of respiratory function due to smooth muscle cell proliferation

Tufts CTSI

Pathophysiology of Asthma in Humans

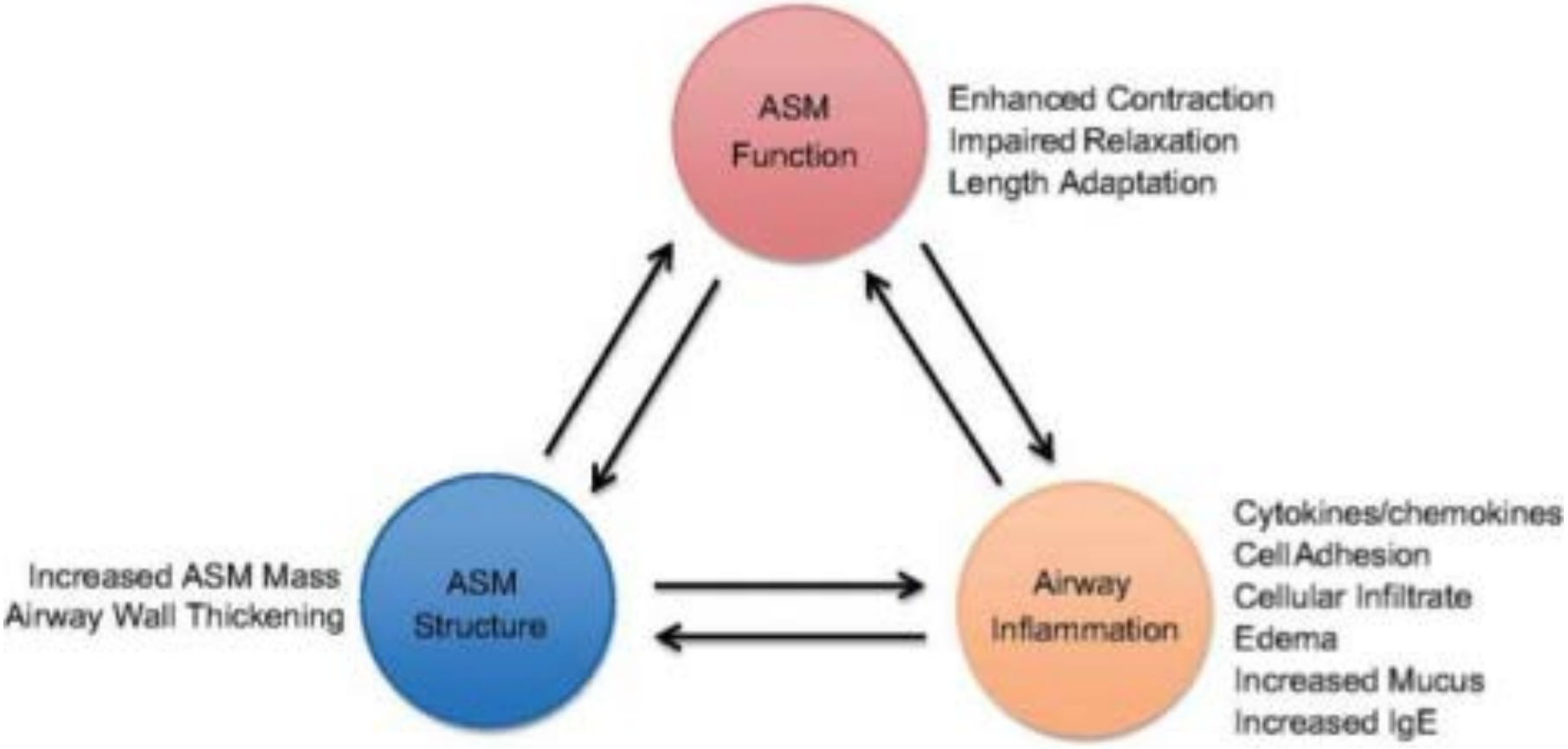
- Allergic v. non-allergic
- Chronic airway inflammation
- Smooth muscle proliferation
- Heightened response to environmental triggers
- Episodes of bronchoconstriction with reversible airflow obstruction



Diana C. Doeing, and Julian Solway J Appl Physiol 2013;114:834-843

Tufts CTSI

Airway Smooth Muscle and Asthma



Diana C. Doeing, and Julian Solway J Appl Physiol 2013;114:834-843

Tufts CTSI

Asthma Treatment

- Reverse acute bronchoconstriction – bronchodilators
- Decrease inflammation – corticosteroids
- Modulate environment – decrease exposure to triggers

Asthma is not just a human problem!

- Horses
  - Inflammatory airway disease
  - Heaves
- Cats
  - Feline asthma

Excess accumulation of airway smooth muscle cells is a prominent feature of airway wall remodeling in both animals and people

Tufts CTSI

Clinical Manifestations of Disease in Human, Horse and Cat

- Reversible airway obstruction
- Airway hyper-responsiveness
- Cough
- Wheeze
- Exercise impairment

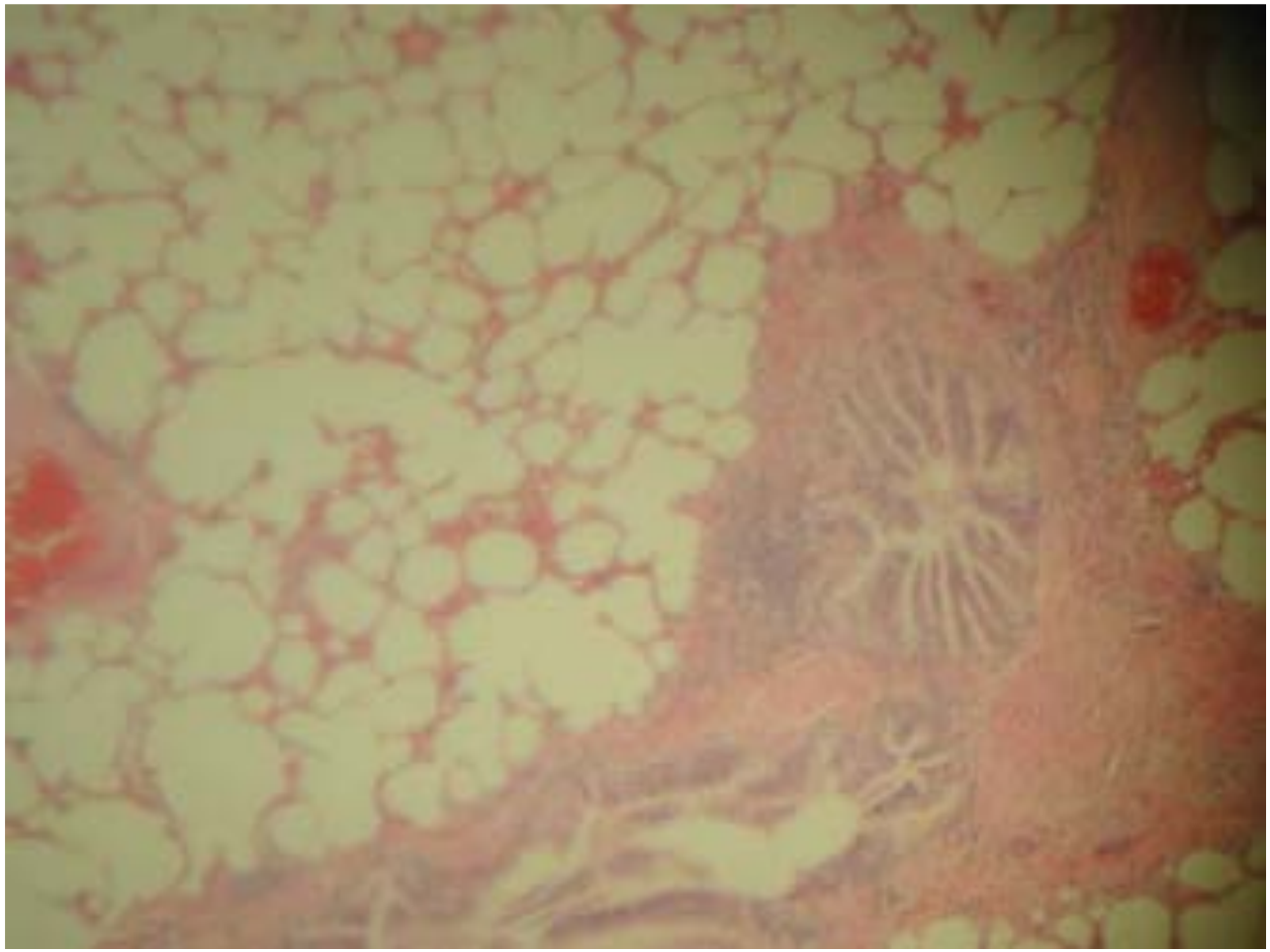
Horse with Equine Asthma

Tufts CTSI

Cat With Feline Asthma

Tufts CTSI

Smooth Muscle Hyperplasia - Horse



Tufts CTSI

Treatment – B2AR and corticosteroids- does not address ASM hypertrophy

Tufts CTSI

What makes horses and cats good models?

Horse

- LARGE – easy to sample airways tissues and secretions over time
- Direct visualization of airways with bronchoscopy
- Pulmonary function testing commonly performed

Cat

- SMALL – can readily assess with CT

Both have clinical signs similar to humans. Rodents do not.

Tufts CTSI

Pharmacological Targeting of ASM

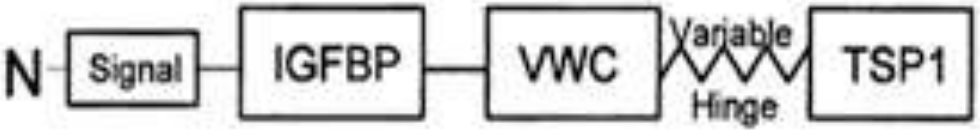
- No effective strategies to decrease ASM proliferation
- CCN5 protein inhibits proliferation of cultured human ASM, as well as human vascular and fibroid smooth muscle cell proliferation
- CCN5 expression is high in healthy airways and virtually absent in asthmatic airways in mice
- Human ASM treated with CCN5 or calcium channel blockers (CCBs) display similar gene expression profiles, based on Connectivity analysis
- CCBs are cheap and have a favorable toxicity profile

Tufts CTSI

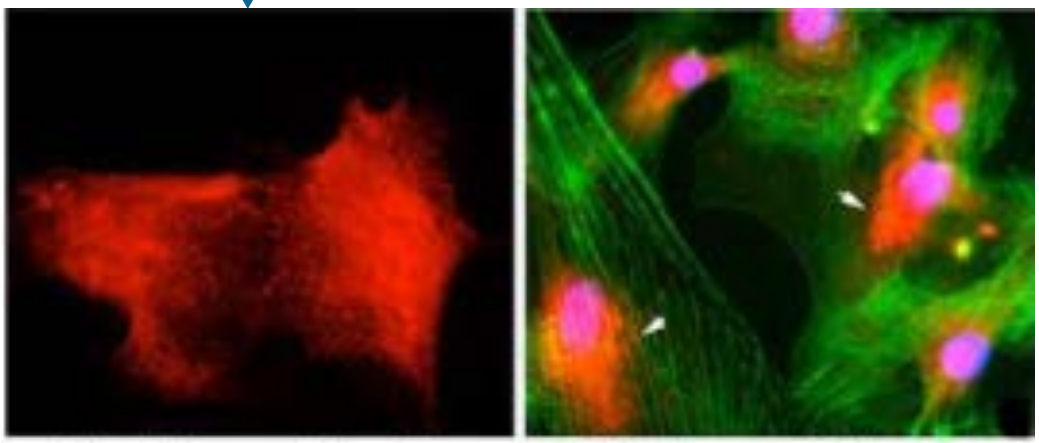
CCN5

CCN1 (CYR61)
CCN2 (CTGF)
CCN3 (NOV)
CCN4 (Wisp-1)
CCN6 (Wisp-3)

CCN5 (COP-1)



- 28kD, cystein-rich protein found in many cells and tissues
- Matricellular and nuclear protein



Non-Permeabilized

Membrane Extracted

Confocal/DIC merge

Hypothesis

The use of clinically relevant animal models of human asthma will allow us to detect the clinical efficacy of CCN5 and CCN5-mimetic CCBs in limiting airway remodeling and damage by reducing ASM hyperplasia, acute bronchospasm, and inflammation, thus protecting pulmonary function.

Tufts CTSI

Aim 1

Determine the differential expression of CCN5 in horses and cats with clinically documented naturally occurring asthma vs. non-asthma

- PFTs
- BAL
- Endobronchial biopsy
- Brush biopsy

Tufts CTSI

Aim 2

Determine the effect of CCN5 and CCBs on cultured ASM from horses and cats with well-characterized asthma.

- Infect cultured ASM cells from horses and cats with:
  - Adenoviral vector expressing CCN5
  - Verapamil, diltiazem and nifedipine representing 3 classes of CCBs
- Measure cell proliferation and cell death

Tufts CTSI

Thank You

Tufts CTSI

Discussants

Sucharita Kher, MD

Alejandro Moreno-Koehler, MPH

John Castellot, PhD

Tufts CTSI

Questions?

Tufts CTSI

Break!

The Effects of Antimicrobial Therapy in Dogs on Owner Microbiota

Shira Doron MD, FIDSA
Kirthana R. Beaulac, PharmD BCPS
Tine Vindenes MD
Annie Wayne DVM, MPH

Tufts Medical Center
Foster Hospital for Small Animals at the Cummings School of Veterinary Medicine

Tufts CTSI

Transmission of MRSA between Companion Animals and Infected Human Patients Presenting to Outpatient

Phylogenetic and Pathotypic Similarities between *Escherichia coli* Isolates from Urinary Tract Infections in Dogs and Extraintestinal Infections in Humans

James R. Johnson,[1,3] Adam L. Stell,[1,3] Parissa Delavari,[1,3,4] Andrew C. Murray,[1,3,4] Michael Kuskowski,[2,4] and Wim Gaastra[5]

[1]*Medical Service and* [2]*Geriatric Research, Education, and Clinical Center, Minneapolis Veterans Affairs Medical Center, and Departments of* [3]*Medicine and* [4]*Psychiatry, University of Minnesota, Minneapolis;* [5]*Department of Bacteriology, Institute of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, University of Utrecht, Utrecht, The Netherlands*

Characterization of Tn*1546* in Vancomycin-Resistant *Enterococcus faecium* Isolated from Canine Urinary Tract Infections: Evidence of Gene Exchange between Human and Animal Enterococci

S. Simjee[1,*], D. G. White[1], P. F. McDermott[1], D. D. Wagner[1], M. J. Zervos[2], S. M. Donabedian[2], L. L. English[1], J. R. Hayes[1,3] and R. D. Walker[1]

J.S. Weese[a,*], H. Dick[b], B.M. Willey[c], A. McGeer[c], B.N. Kreiswirth[d], B. Innis[e], D.E. Low[c]

Commonly Prescribed Antibiotics

In dogs and cats:

- Amoxicillin and amoxicillin-clavulanic acid
- Cephalexin
- Doxycycline
- Enrofloxacin (fluoroquinolone)
- Clindamycin
- Metronidazole

In humans:

- Amoxicillin and amoxicillin-clavulanic acid
- Cephalexin
- Doxycycline, minocycline
- Ciprofloxacin (fluoroquinolone)
- Clindamycin
- Metronidazole

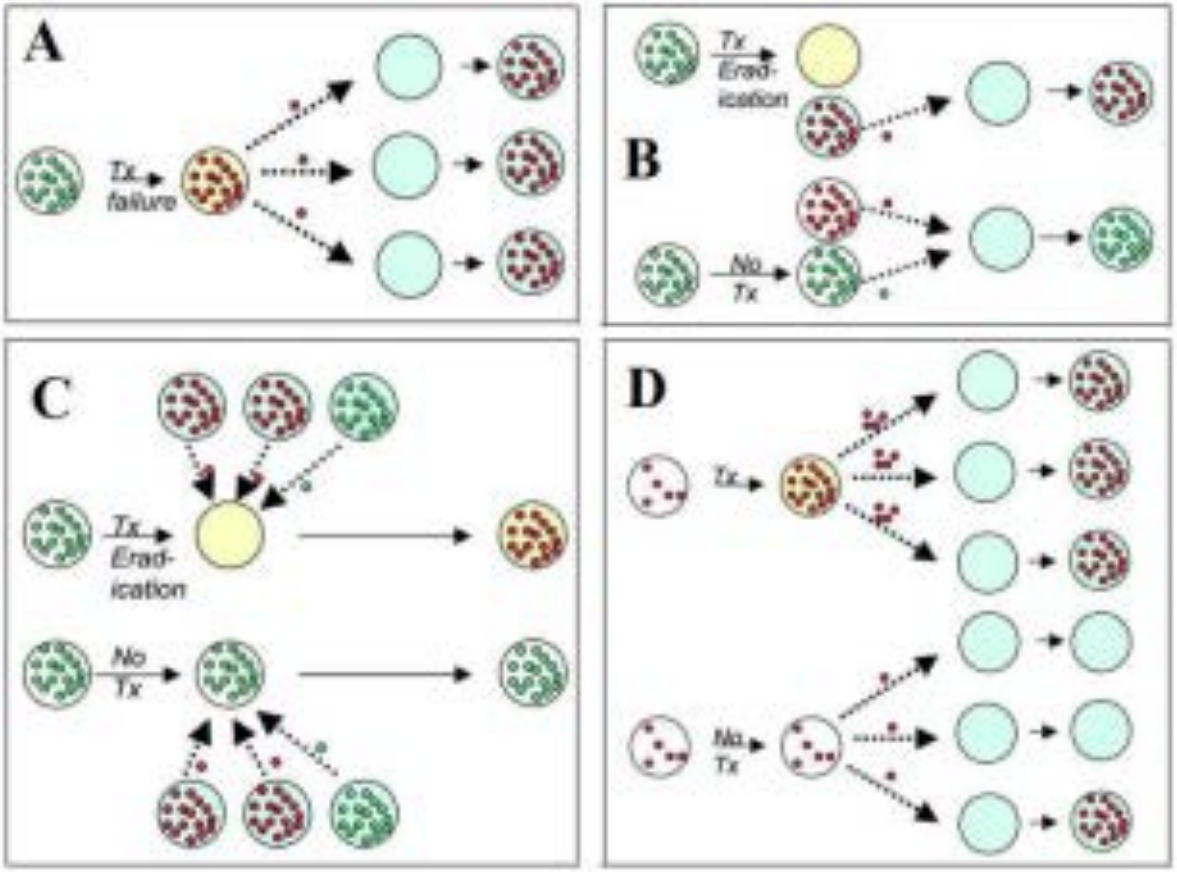
Tufts CTSI

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”

- Alexander Fleming, 1945

Tufts CTSI

Antibiotic Use Causes Resistance



Lipsitch M, Samore MH. *Emerg Inf Dis*. 2002; 8(4):347-354.

Tufts CTSI

Collateral Damage

Cephalosporins

- Vancomycin-resistant *Enterococci*
- Methicillin-resistant *Staphylococcus aureus*
- Extended-spectrum β-lactamase producing *Klebsiella pneumoniae*
- Multidrug-resistant *Acinetobacter baumanii*

Fluoroquinolones

- Methicillin-resistant *Staphylococcus aureus*
- Fluoroquinolone-resistant gram-negative bacilli
  - *E. coli* resistance in the community
  - *Pseudomonas aeruginosa* resistance in hospitals
- Extended-spectrum β-lactamase producing organisms

Tufts CTSI

Paterson DL. *Clin Inf Dis*. 2004; 38 (Suppl 4)S341-5.

The Microbiome

- The GI microbiota serves many important functions including maintenance of nutrition, innate immunity, intestinal barrier function and preventing colonization by pathogens.
- Dethlefson *et al* showed that administration of ciprofloxacin decreased the taxonomic richness, diversity and evenness of the microbial community.
- Several taxa failed to normalize even six months later.

Tufts CTSI

Dethlefsen et al. PLoS Biol **2008 Nov 18**; 6(11):e280.

- The GI micr… functions including m… immunity, intestinal ba… olonization by pathogens.
- Dethlefson… n of ciprofloxaci… nness, diversity and evenne…
- Several tax… months later.

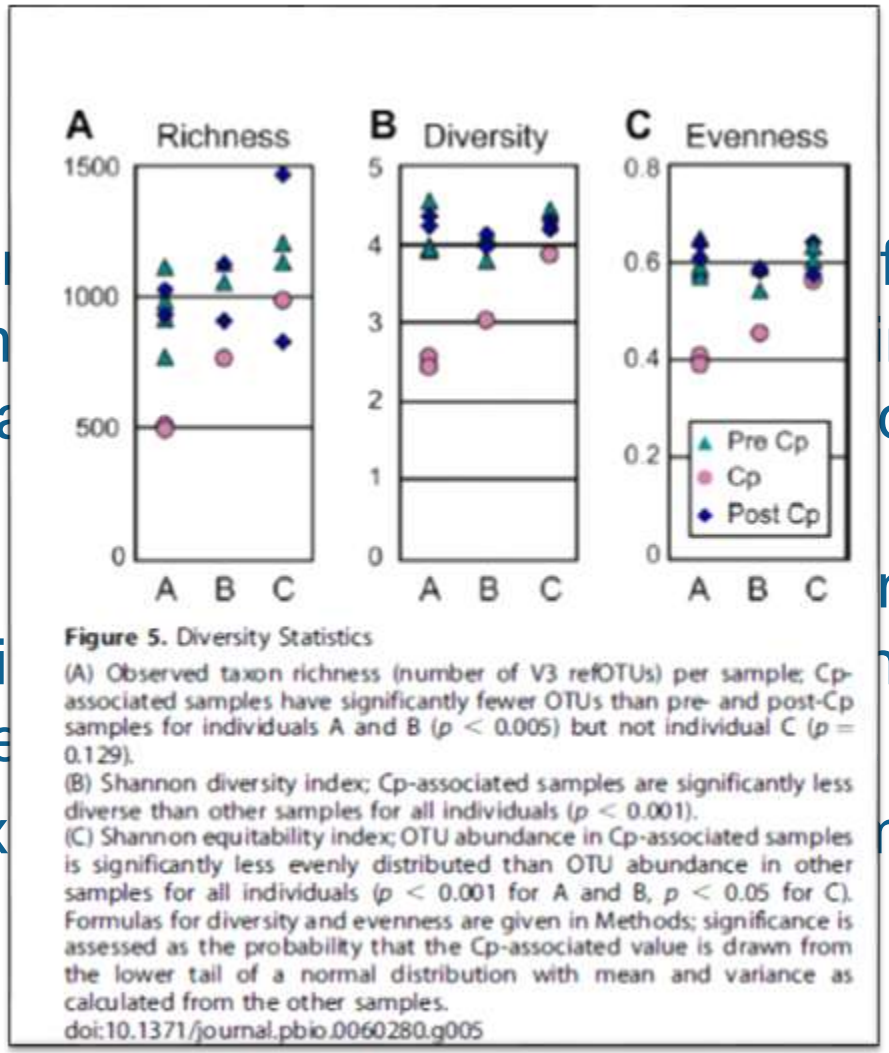


Figure 5. Diversity Statistics

(A) Observed taxon richness (number of V3 refOTUs) per sample; Cp-associated samples have significantly fewer OTUs than pre- and post-Cp samples for individuals A and B ($p < 0.005$) but not individual C ($p = 0.129$).

(B) Shannon diversity index; Cp-associated samples are significantly less diverse than other samples for all individuals ($p < 0.001$).

(C) Shannon equitability index; OTU abundance in Cp-associated samples is significantly less evenly distributed than OTU abundance in other samples for all individuals ($p < 0.001$ for A and B, $p < 0.05$ for C). Formulas for diversity and evenness are given in Methods; significance is assessed as the probability that the Cp-associated value is drawn from the lower tail of a normal distribution with mean and variance as calculated from the other samples.

doi:10.1371/journal.pbio.0060280.g005

Tufts CTSI

Dethlefsen et al. PLoS Biol **2008 Nov 18**; 6(11):e280.

Antibiotic Effects

- Jernberg et al demonstrated highly significant disturbances in bacterial communities that persisted over a two-year period after a seven-day course of clindamycin
- In particular, they found a sharp decline in the clonal diversity of Bacteroides and persistence of highly resistant clones

Tufts CTSI

Jernberg et al. The ISME Journal **2007 (1):** 56-66

- Jernberg et ant disturbance persisted over a two-year p e of clindamicin
- In particular the clonal diversity of highly resistant clo

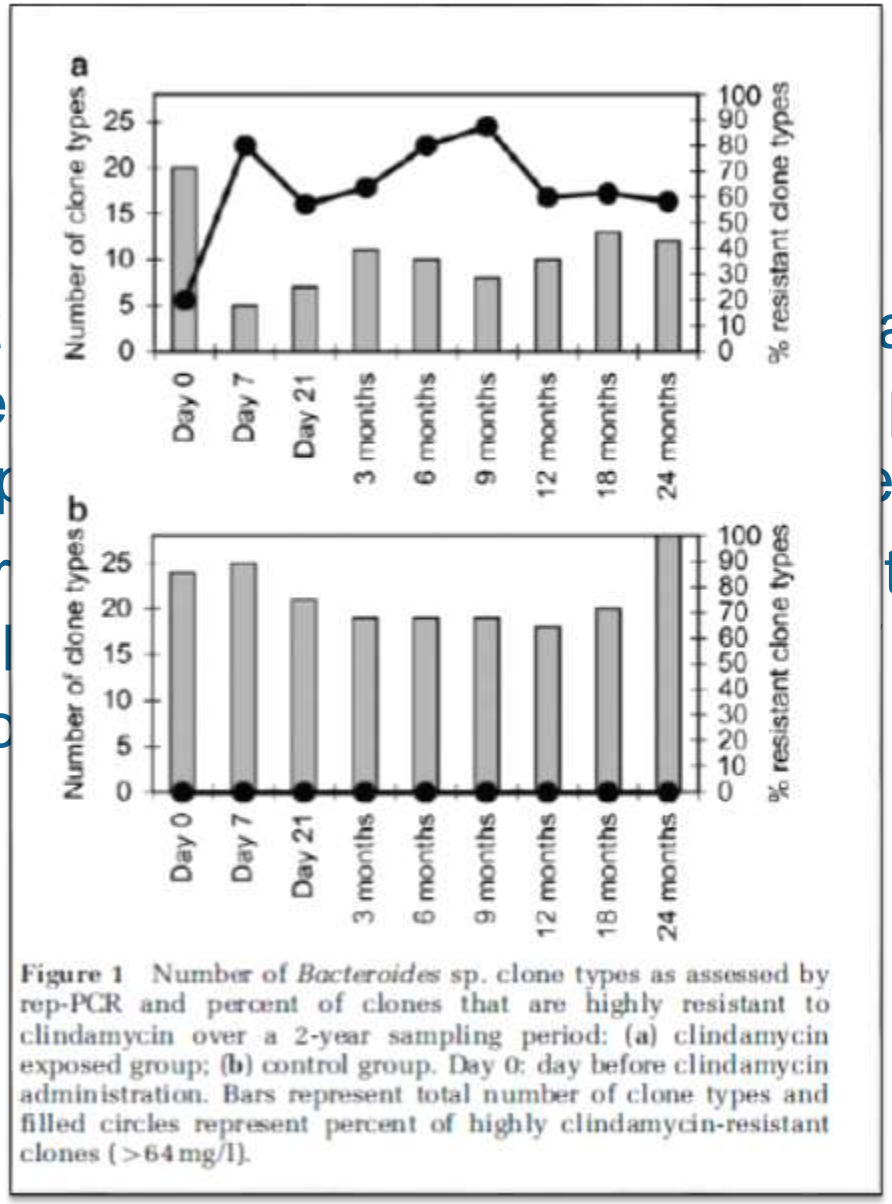


Figure 1 Number of *Bacteroides* sp. clone types as assessed by rep-PCR and percent of clones that are highly resistant to clindamycin over a 2-year sampling period: (**a**) clindamycin exposed group; (**b**) control group. Day 0: day before clindamycin administration. Bars represent total number of clone types and filled circles represent percent of highly clindamycin-resistant clones (>64 mg/l).

Tufts CTSI

Jernberg et al. The ISME Journal **2007 (1):** 56-66

Transfer of the Microbiome Between Pets and Humans

- Oh *et al* used 16S rDNA pyrosequencing to compare the oral microbiomes of pets with their owners
- Results were mixed. Owner-pet pairs with high "closeness scores" indicating oral contact were more likely to have similarities

Tufts CTSI

Oh et al. PLOS One **2015 July 2** (10)7: e0131468

Methods

- Enroll 20 pet-owner pairs in which the pet is treated with an outpatient course of antibiotics for any indication
- Enroll 20 pet-owner pairs as controls (no antibiotics)
- Baseline oral/fecal samples, repeat after antibiotics
- Assess changes in microbial composition in the animal and the human

Tufts CTSI

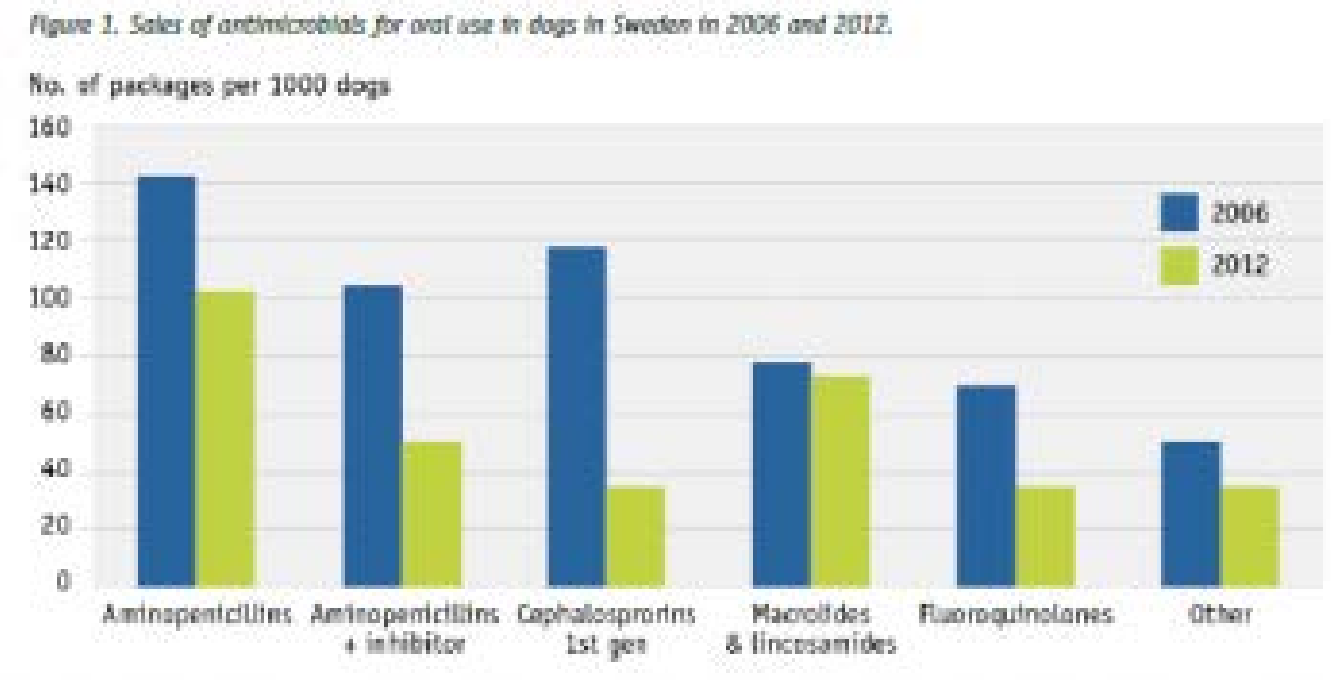
Hypotheses

- The bacterial composition of the mouth/stool will change in the pet as a result of antibiotic administration
- The bacterial composition of the mouth/stool will change in the owner as a result of antibiotic administration to the pet

Tufts CTSI

Significance

- Pets consume 150,000 kg of antibiotics annually in the United States



Tufts CTSI

Hollis A, Ahmed Z. *NEJM*. 2013; 369(26):2474-2476.
Grecko C. *Eur J Comp Anim Pract*. 2013; 23(4): 55-60.

US CDC. Antimicrobial Resistance Threats, 2013. 2014.

Questions for the group

- Species: limit to dogs only?
- Human cohort: adults versus babies (microbiome not yet established)?
- Pyrosequencing versus culture-based versus repetitive sequence based PCR versus T-RFLP as outcomes?
- Limit to high “closeness score”
- Oral versus fecal microbial composition?

Tufts CTSI

Questions for the group

- Antibiotic: limit to beta-lactams (most commonly used)? Include a fluoroquinolone arm?
- Duration of antibiotic therapy?
- Timing of follow-up specimen?
- Incentives for participation?

Tufts CTSI

Thank You

Tufts CTSI

Discussants

Cheleste Thorpe, MD

Farzad Noubary, PhD

Deborah Kochevar, DVM, PhD, DACVC

Tufts CTSI

Questions?

Tufts CTSI

Cohabitation with Production Animals, Gut Microbiota, and Stunting in Guatemalan Children

Marieke Rosenbaum, DVM, MPH (Co-I | TCSVM)

Janet Forrester, PhD, MSc (PI | PHPD)

Honorine Ward, MBBS (Co-I | SSBS)

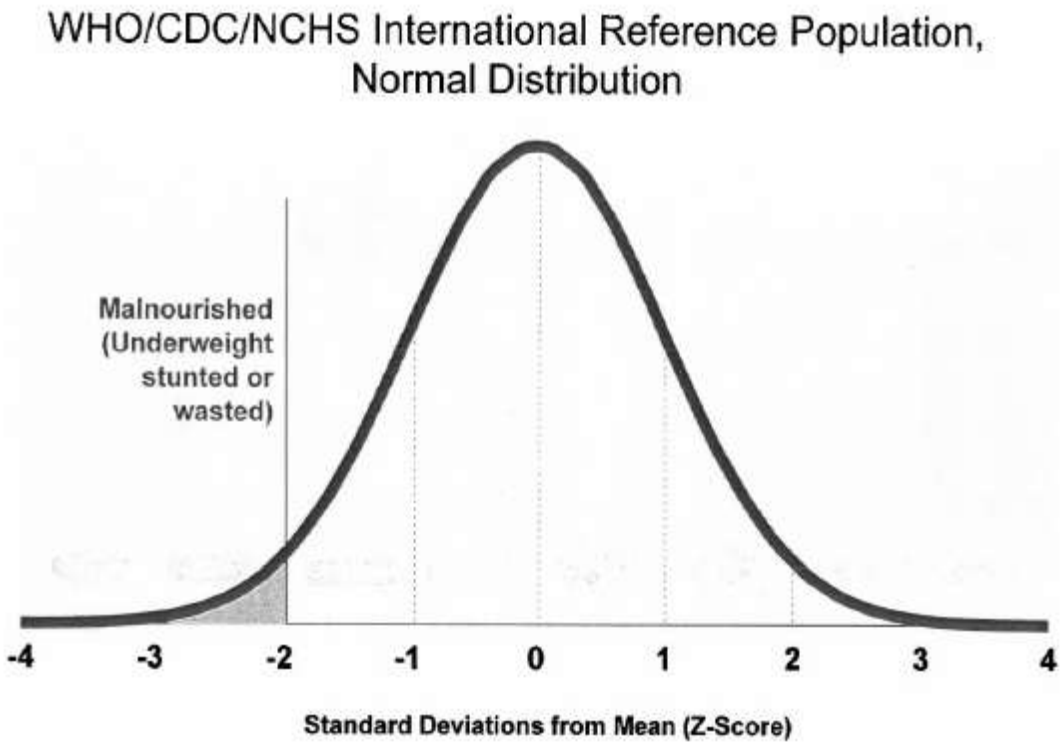
Noel Solomons, MD (Co-I | Friedman, CeSSIAM)

Henry Rogalin, PhD (Post Doc | CTSI)

What Is Stunting?

What Is Stunting?

Low Height for Age (HAZ) <2 SD Below WHO Median for Optimal Growth.



Why Does Stunting Matter?

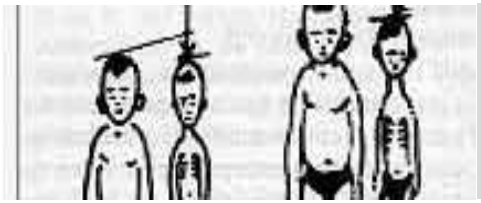
Intellectual Development

Educational Attainment

Economic Development

Longevity

Immune Response



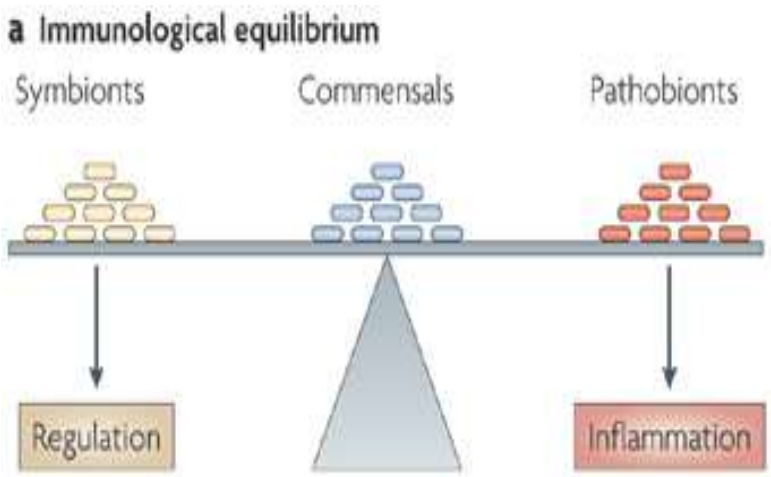
Stunted Offspring

Work Productivity

What Causes Stunting?

Associations With Stunting

- Maternal Health
- Parasitic Infections
- Gut Microbial Composition
- Poor Sanitation
- Impaired Intestinal Integrity
- Nutrition

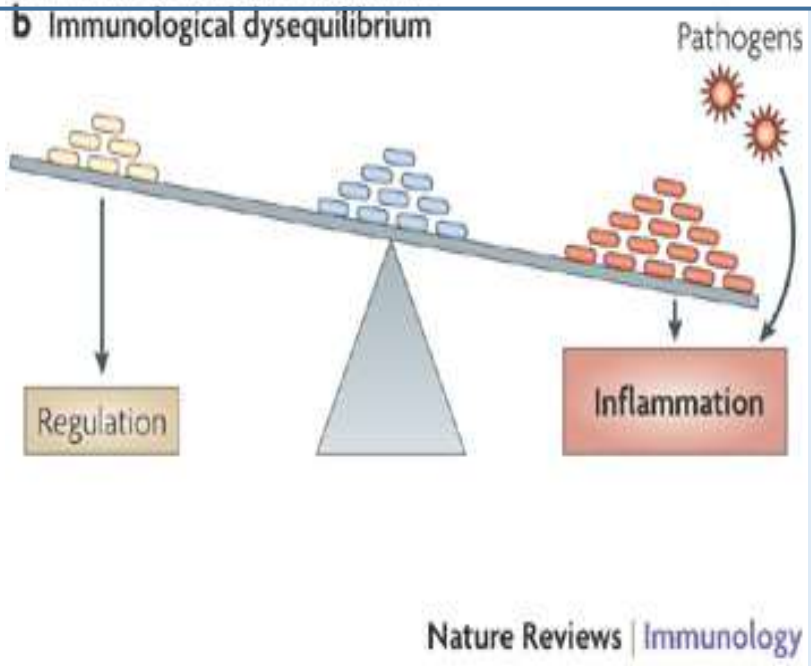


Nutritional Status

Intestinal Integrity

Immune Response

Inflammatory Response



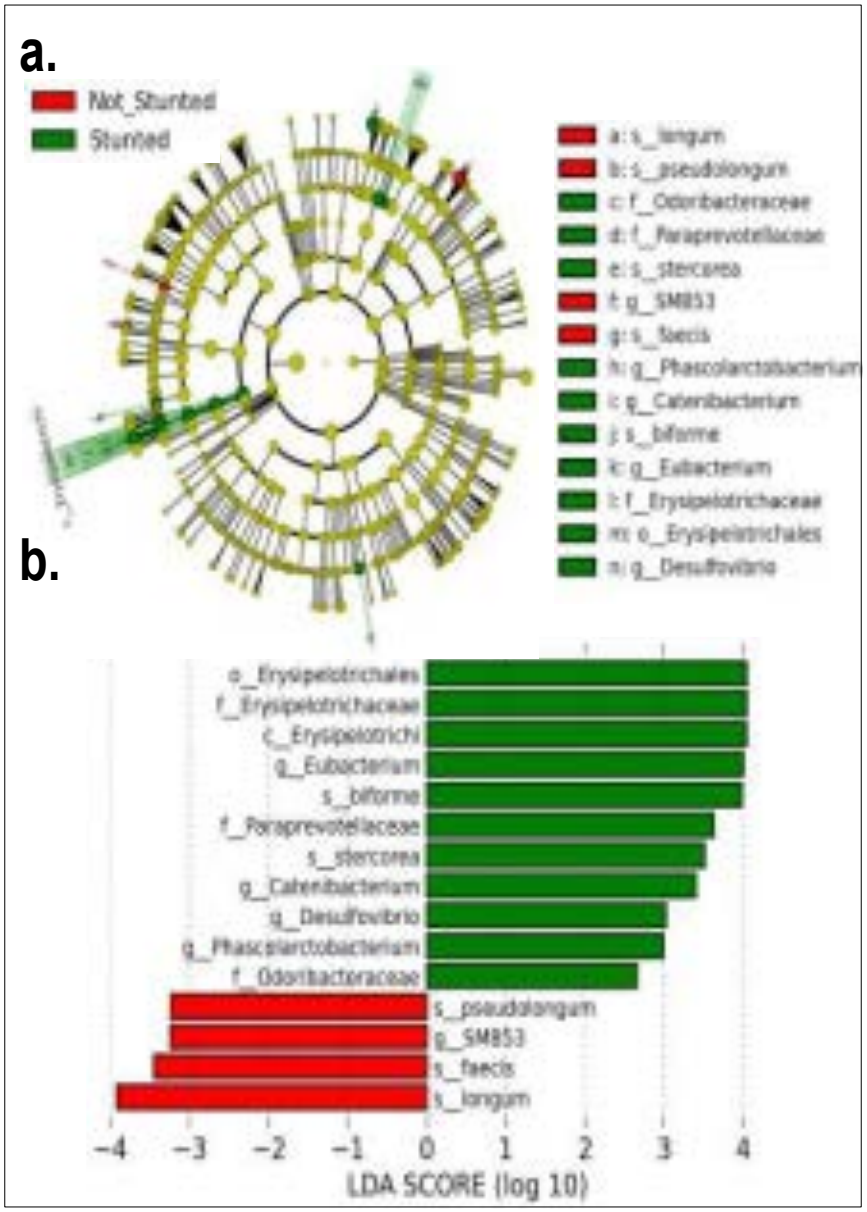
Impaired Intestinal Integrity

Microbial Translocation

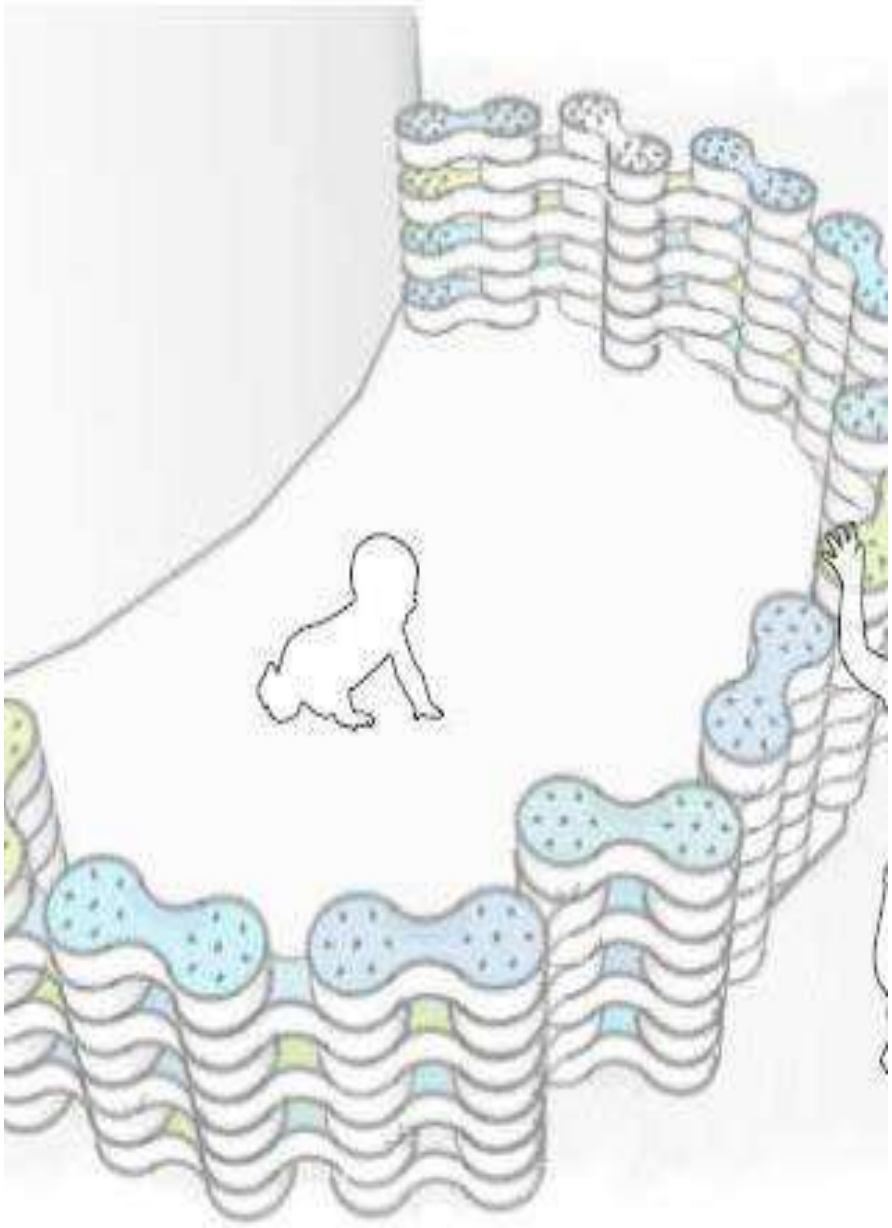
Inflammation

MaInutrition

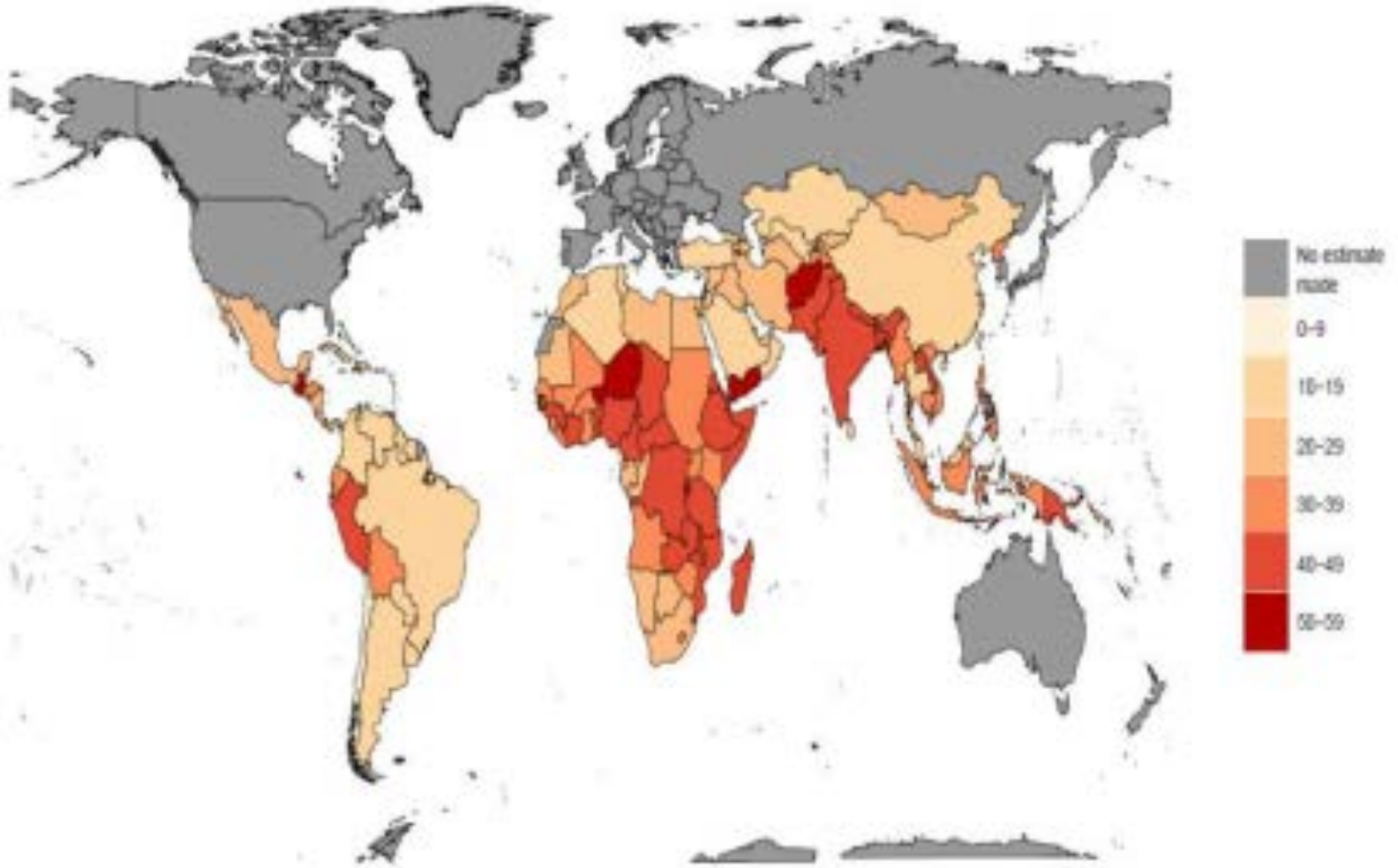
Preliminary Data by Dr. Ward and Dr. Kang from Vellore, India



Does exposure to animal feces, through alterations in the gut microbiota, promote stunting in children?



Map __.1 Prevalence of Stunting by Country, 2011

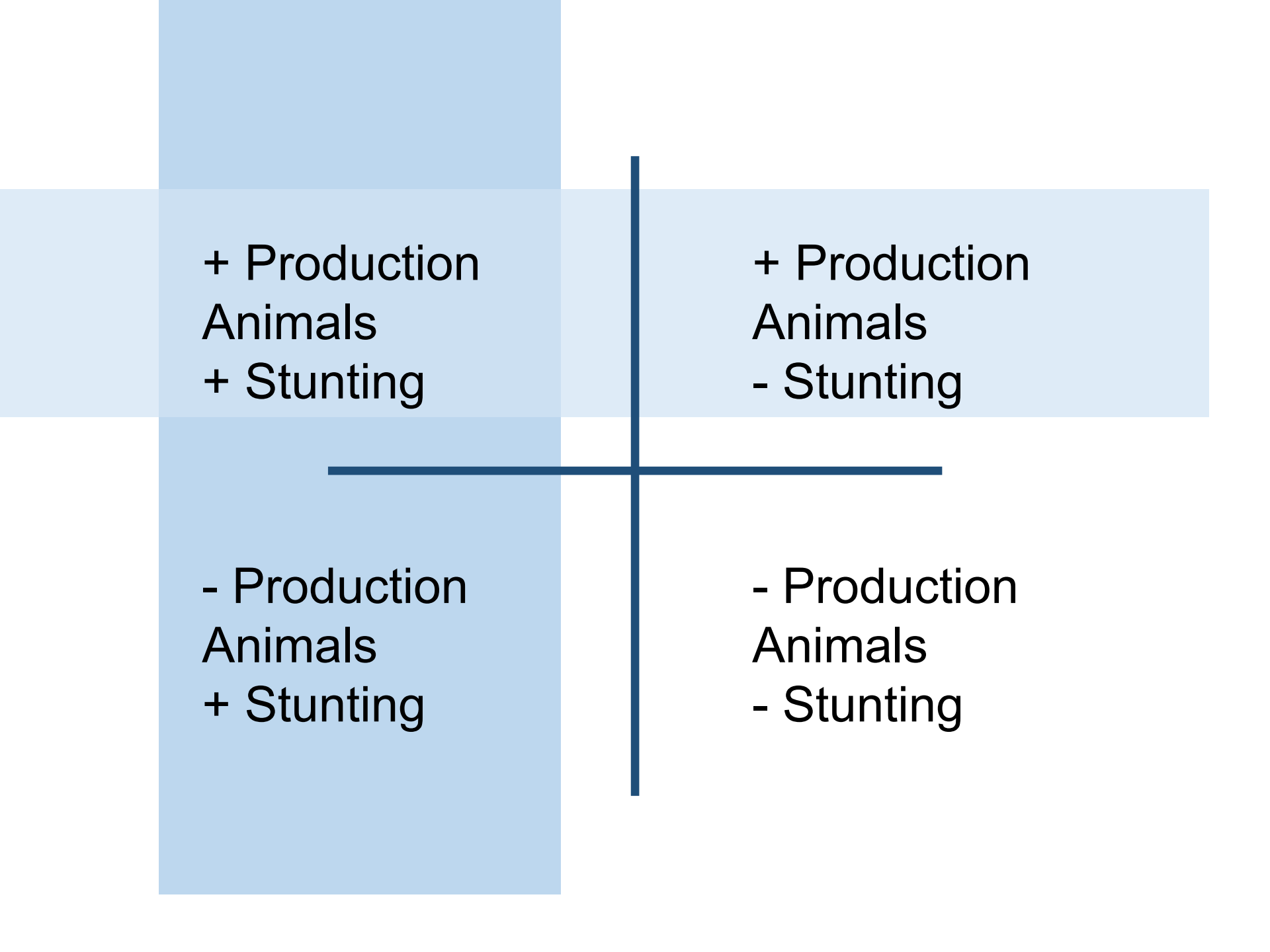


Source: Stevens et al, 2012.

Recent Data on Stunting in Guatemala by Dr. Solomons and Colleagues, 2013

Table 1: Average HAZ scores and proportion of stunted children by subgroups in children attending public health clinics in urban Quetzaltenango & suburban La Esperanza (n=299)

Age	HAZ score (mean, SD)	Proportion stunted (%)
6-11 months (n=114)	-1.70 (1.13)	41/114 (36%)
12-17 months (n=98)	-2.07 (1.16)	53/98 (54%)
18-23 months (n=87)	-1.93 (0.98)	41/87 (47%)


+ Production Animals + Stunting
+ Production Animals - Stunting
- Production Animals + Stunting
- Production Animals - Stunting

Thank You

Tufts CTSI

Discussants

Shibani Ghosh, PhD

Janis Breeze, MPH

Nicholas Frank, DVM, PhD, DACVIM

Tufts CTSI

Questions?

Tufts CTSI

Breakout Sessions

Goals:

- Add, delete, change Specific Aims
- List of additional experiments/experimental approaches that would enhance project impact
- List of preliminary data needed before submission
- List additional collaborators needed for team
- List next steps for team

Tufts CTSI

Workgroups

Workgroup	Room
Development of a Safe, Inexpensive, Easily Administered EHEC Vaccine for Cattle John Leong, MD, PhD	**Room 1414**
A Novel Approach to Asthma Therapy: Decreasing Airway Smooth Muscle Mass Melissa Mazan, DVM, DACVIM	**Room 1503**
Antibiotic Stewardship and Infection Control Shira Doron, MD	**Room 1533**
Cohabitation with Production Animals, Gut Microbiota, and Stunting in Children Marieke Rosenbaum, DVM, MPH	**Room 1521**

Tufts CTSI

Report Back

Breakout Session Goals:

- Add, delete, change Specific Aims
- List of additional experiments/experimental approaches that would enhance project impact
- List of preliminary data needed before submission
- List additional collaborators needed for team
- List next steps for team

Tufts CTSI

Thank you very much!

Tufts CTSI

One Health Symposium

Tufts CTSI