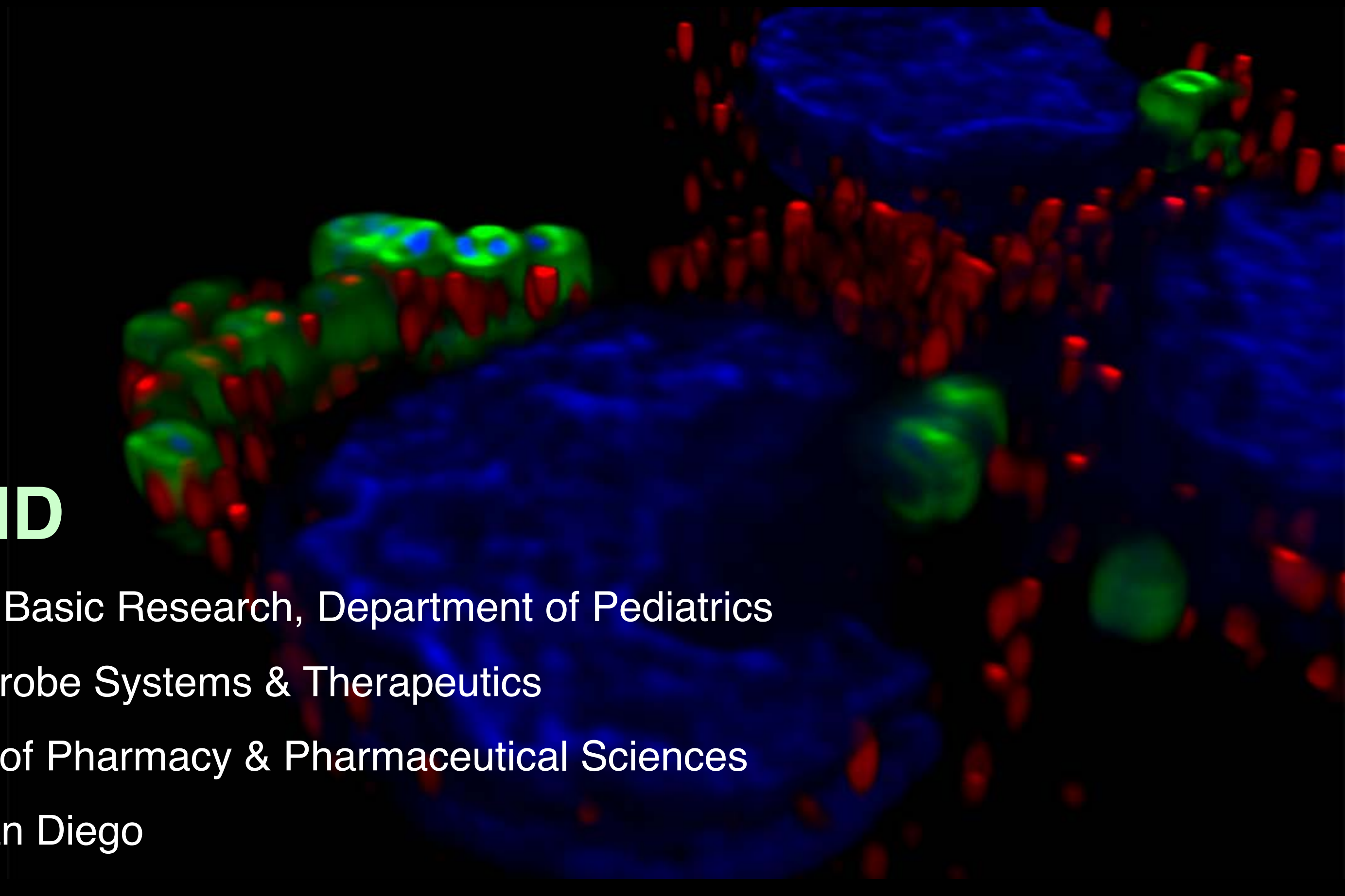
REDEFINING AND REINVENTING "ANTIBIOTICS" TO COMBAT THE SUPERBUG CRISIS



Victor Nizet, MD

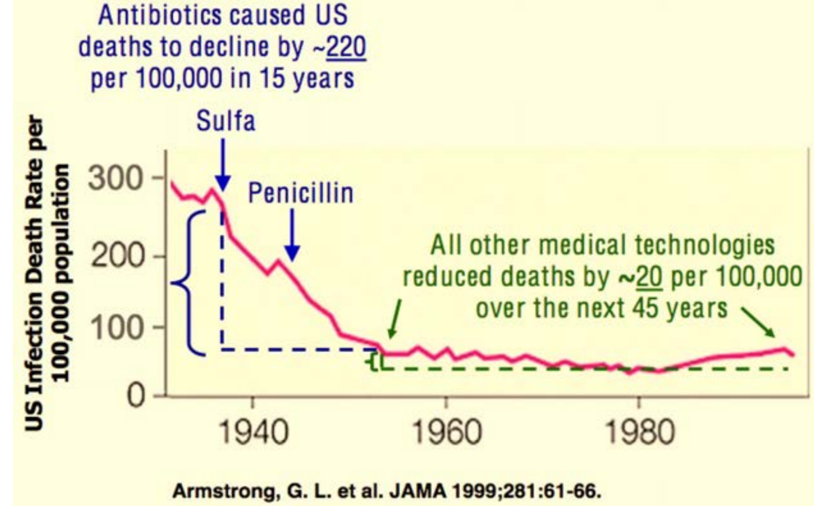
Professor & Vice Chair for Basic Research, Department of Pediatrics

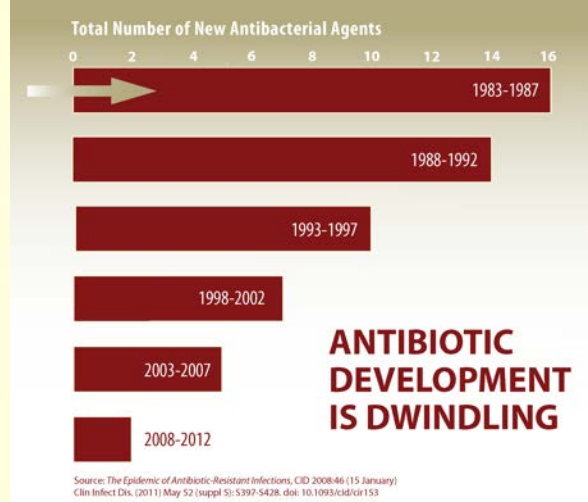
Chief, Division of Host-Microbe Systems & Therapeutics

Professor, Skaggs School of Pharmacy & Pharmaceutical Sciences

University of California, San Diego

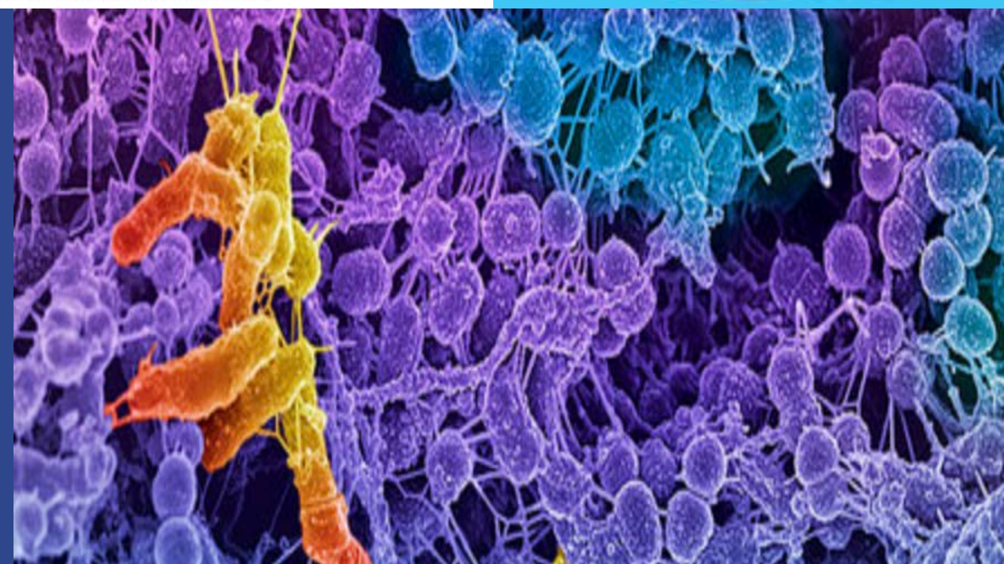
UCSD Town & Gown Luncheon Series | October 10, 2017

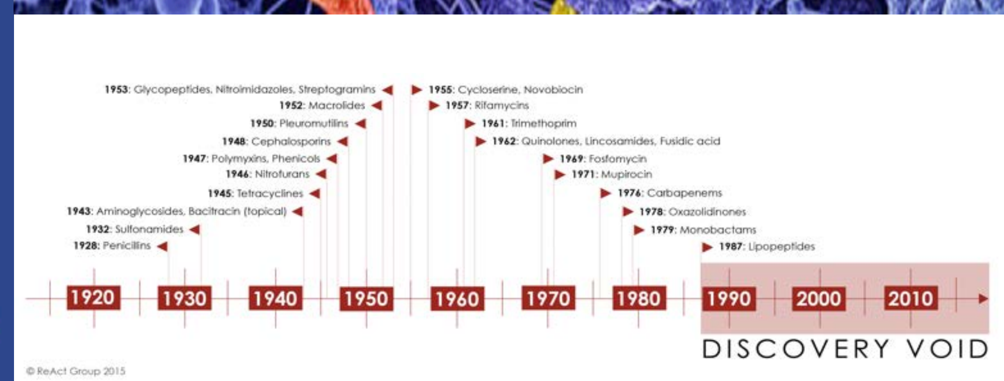

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years
Sulfa
Penicillin
All other medical technologies reduced deaths by ~20 per 100,000 over the next 45 years
US Infection Death Rate per 100,000 population
300
200
100
0
1940
1960
1980
Armstrong, G. L. et al. JAMA 1999;281:61-66.


Total Number of New Antibacterial Agents
0
2
4
6
8
10
12
14
16
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012
ANTIBIOTIC DEVELOPMENT IS DWINDLING
Source: The Epidemic of Antibiotic-Resistant Infections, CID 2008:46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

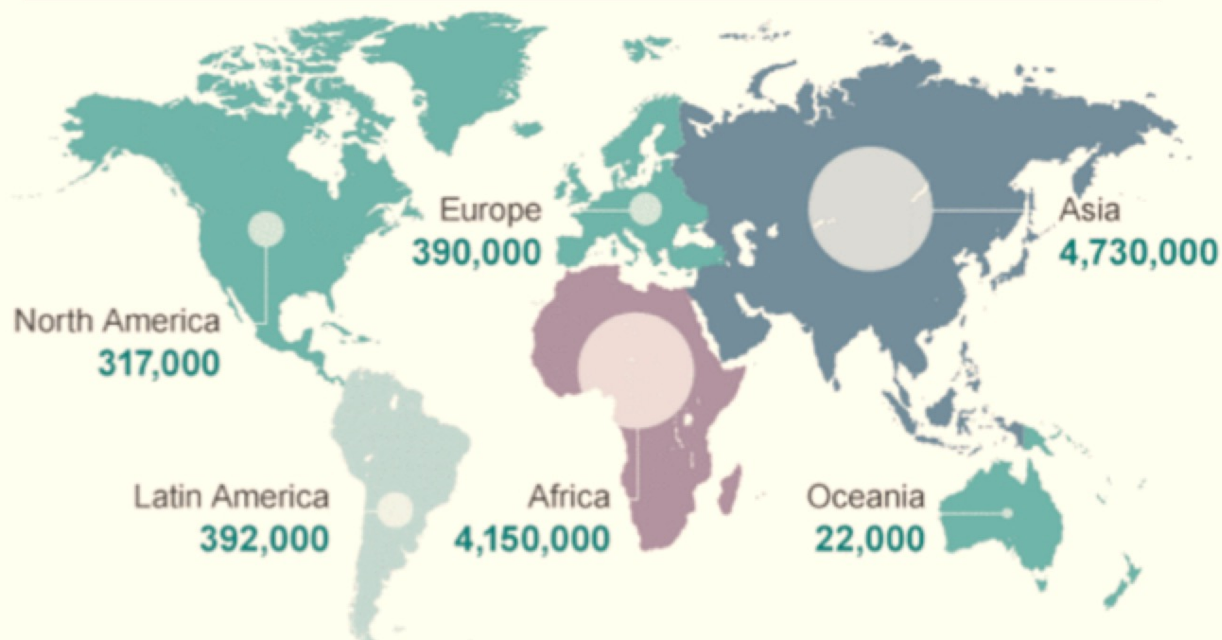

Newsweek
THE DRUGS DON'T WORK
MORE AND MORE DEADLY PATHOGENS ARE BECOMING INCURABLE

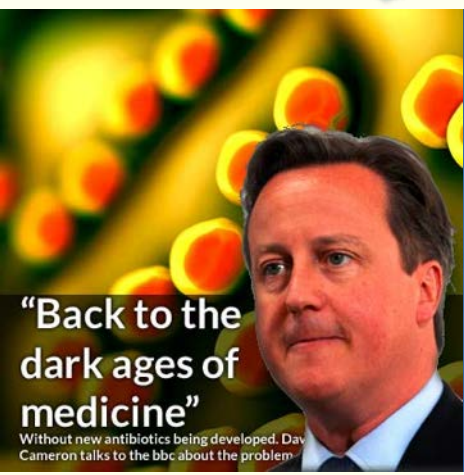

CAUSES OF ANTIBIOTIC RESISTANCE
HANDLE ANTIBIOTICS WITH CARE
Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.
Over-prescribing of antibiotics
Patients not finishing their treatment
Over-use of antibiotics in livestock and fish farming
Poor infection control in hospitals and clinics
Lack of hygiene and poor sanitation
Lack of new antibiotics being developed
www.who.int/drugresistance
#AntibioticResistance
World Health Organization




1953: Glycopeptides, Nitroimidazoles, Streptogramins
1952: Macrolides
1950: Pleuromutilins
1948: Cephalosporins
1947: Polymyxins, Phenicols
1946: Nitrofurans
1945: Tetracyclines
1943: Aminoglycosides, Bacitracin (topical)
1932: Sulfonamides
1928: Penicillins
1955: Cycloserine, Novobiocin
1957: Rifamycins
1961: Trimethoprim
1962: Quinolones, Lincosamides, Fusidic acid
1969: Fosfomycin
1971: Mupirocin
1976: Carbapenems
1978: Oxazolidinones
1979: Monobactams
1987: Lipopeptides
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
DISCOVERY VOID
© ReAct Group 2015

Annual Antibiotic Resistance Deaths by 2050



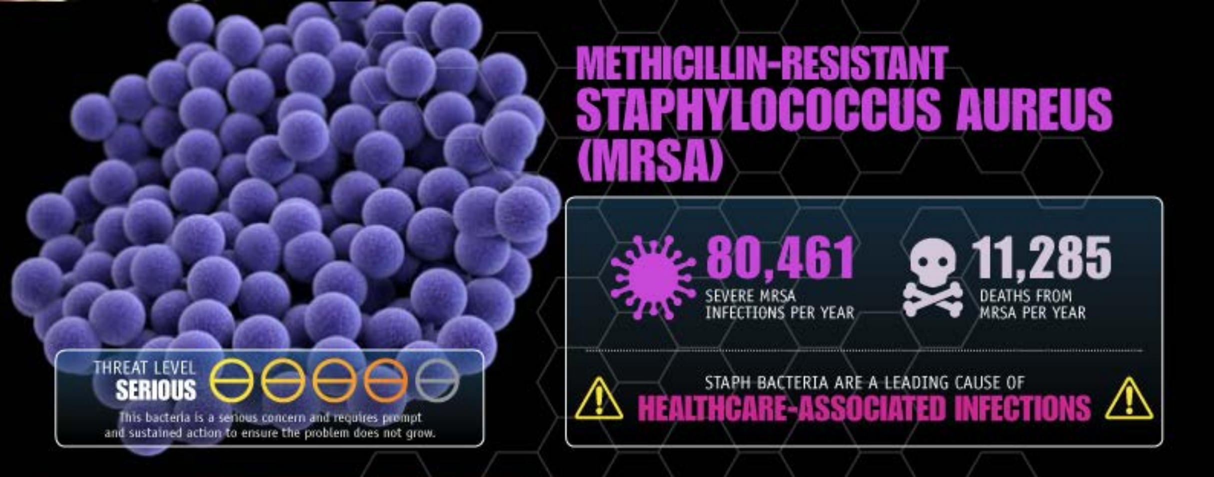


“Resistance will result in $100 trillion in lost economic productivity”

“Antibiotic-resistance is a fundamental threat to global health and safety”

“A National Action Plan to preserve the utility of antibiotics must be enacted”

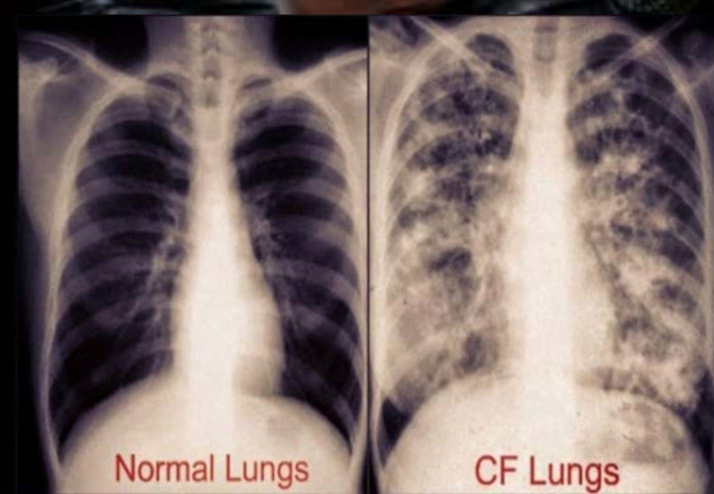
“A post-antibiotic era would mean the end of modern medicine as we know it ”


METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS (MRSA)
80,461
SEVERE MRSA INFECTIONS PER YEAR
11,285
DEATHS FROM MRSA PER YEAR
STAPH BACTERIA ARE A LEADING CAUSE OF
HEALTHCARE-ASSOCIATED INFECTIONS
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.



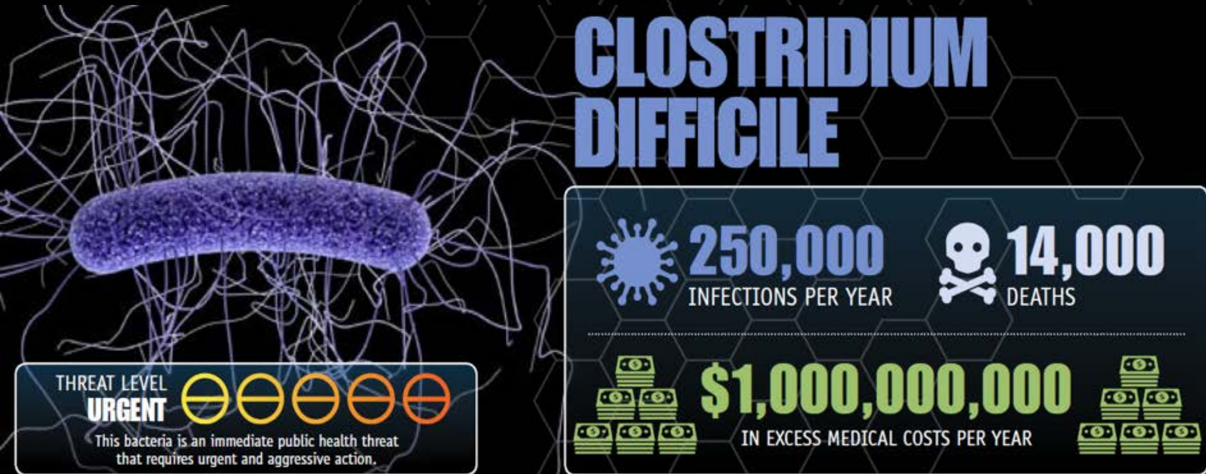
DRUG-RESISTANT
TUBERCULOSIS
1,042
DRUG-RESISTANT TUBERCULOSIS CASES IN 2011 (U.S.)
10,528
TUBERCULOSIS CASES IN 2011 (U.S.)
TUBERCULOSIS IS AMONG THE MOST COMMON INFECTIOUS DISEASES AND
FREQUENT CAUSES OF DEATH WORLDWIDE
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

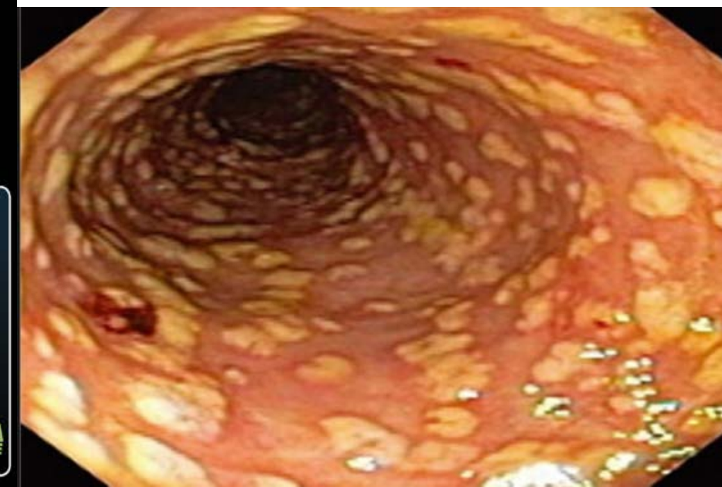


MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA
6,700
MULTIDRUG-RESISTANT PSEUDOMONAS INFECTIONS
440
DEATHS
51,000
PSEUDOMONAS INFECTIONS PER YEAR
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

Normal Lungs
CF Lungs


CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS
CARBAPENEM-RESISTANT KLEBSIELLA SPP. 7,900
1,400 CARBAPENEM-RESISTANT E. COLI
CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.


UCLA SUPERBUG OUTBREAK CAUSED BY DUODENOSCOPE

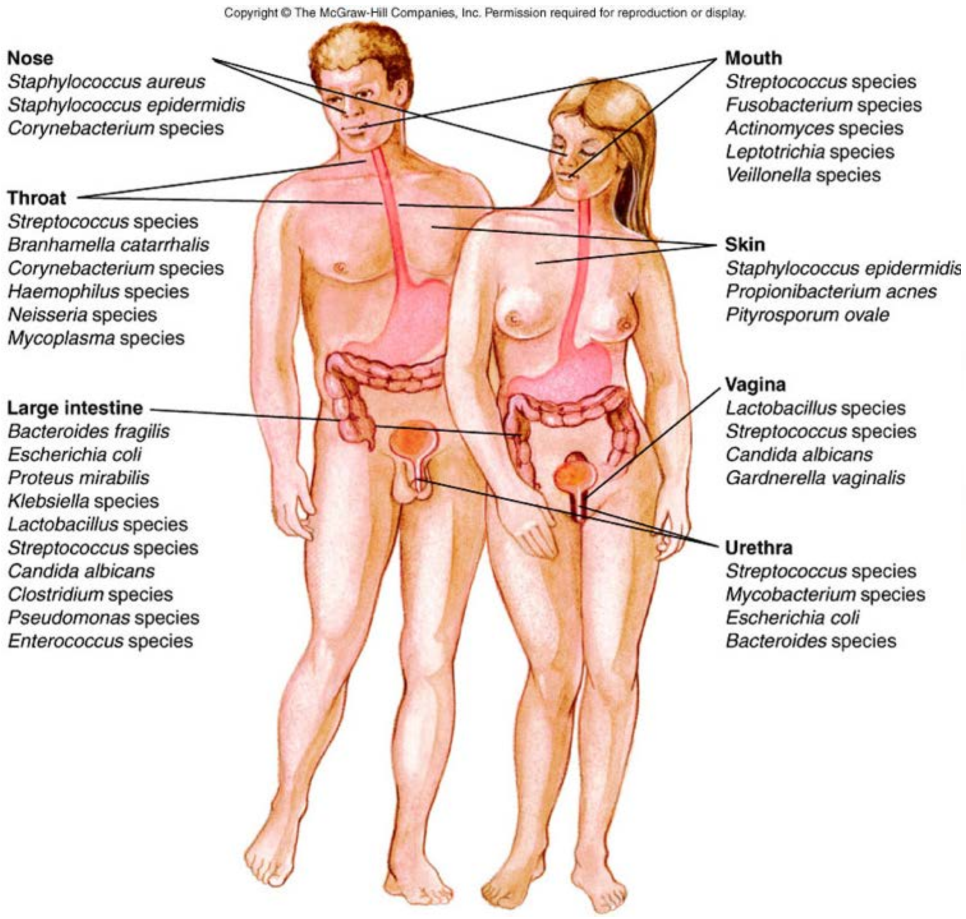

CLOSTRIDIUM DIFFICILE
250,000 INFECTIONS PER YEAR
14,000 DEATHS
$1,000,000,000
IN EXCESS MEDICAL COSTS PER YEAR
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

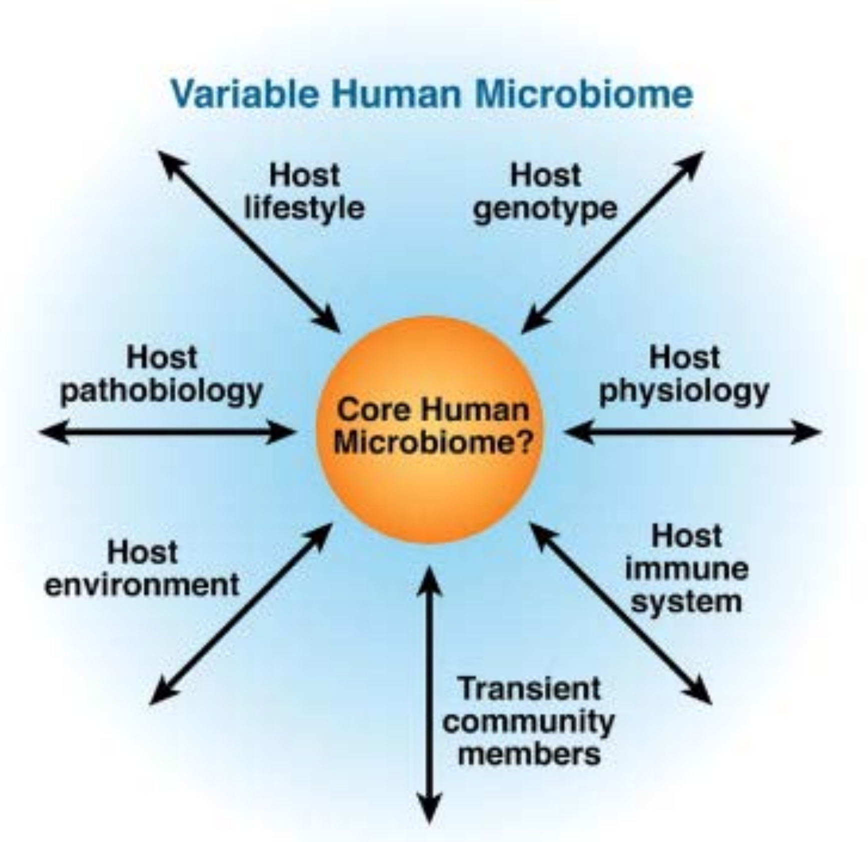


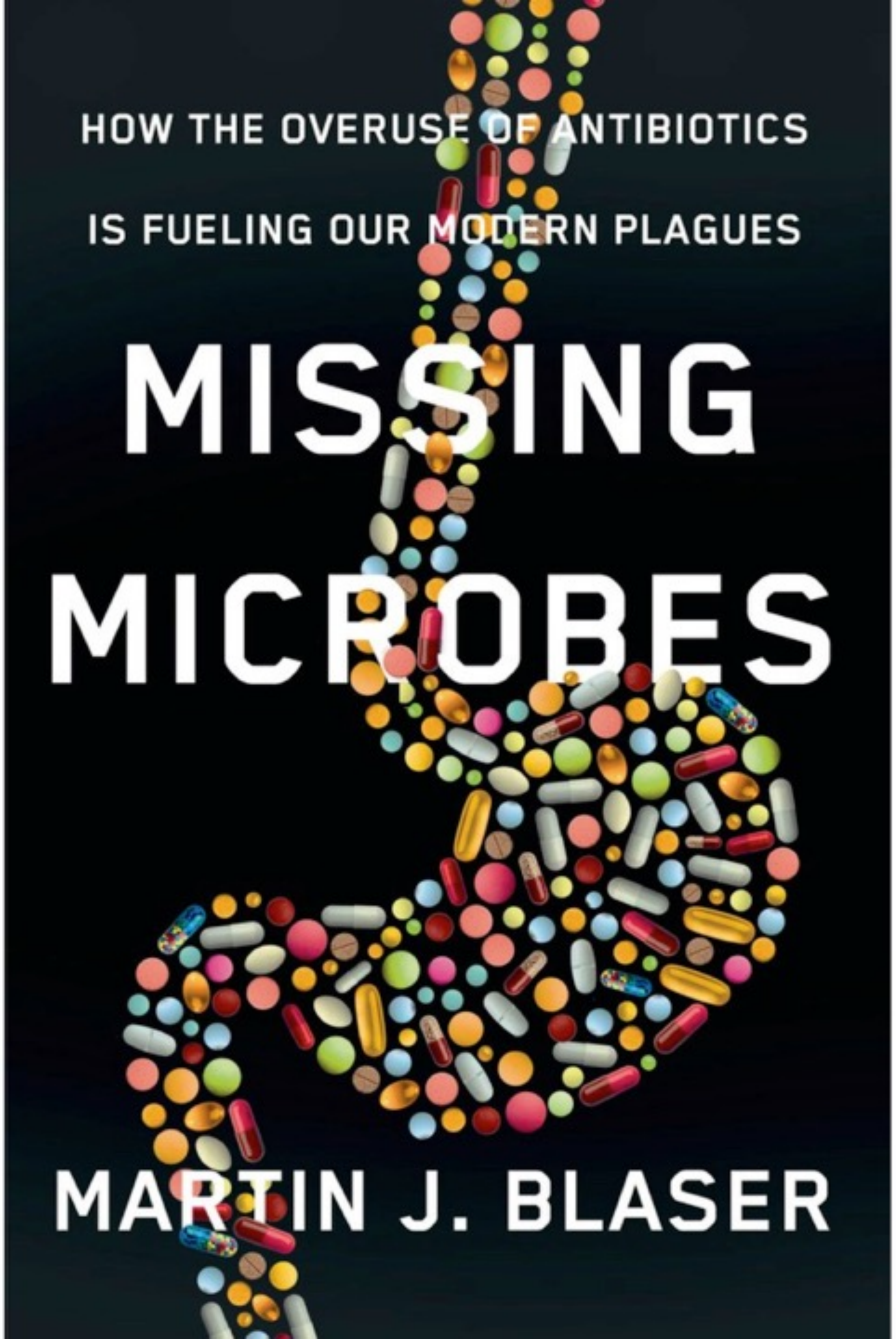

DRUG-RESISTANT
NEISSERIA GONORRHOEAE
246,000 DRUG-RESISTANT GONORRHEA INFECTIONS
188,600 RESISTANCE TO TETRACYCLINE
11,480 REDUCED SUSCEPTIBILITY TO CEFIXIME
3,280 REDUCED SUSCEPTIBILITY TO CEFTRIAXONE
2,460 REDUCED SUSCEPTIBILITY TO AZITHROMYCIN
820,000 GONOCOCCAL INFECTIONS PER YEAR
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.


15-24 year olds account for half of all new STD Infections

The Human Microbiome is Diverse and Dynamic



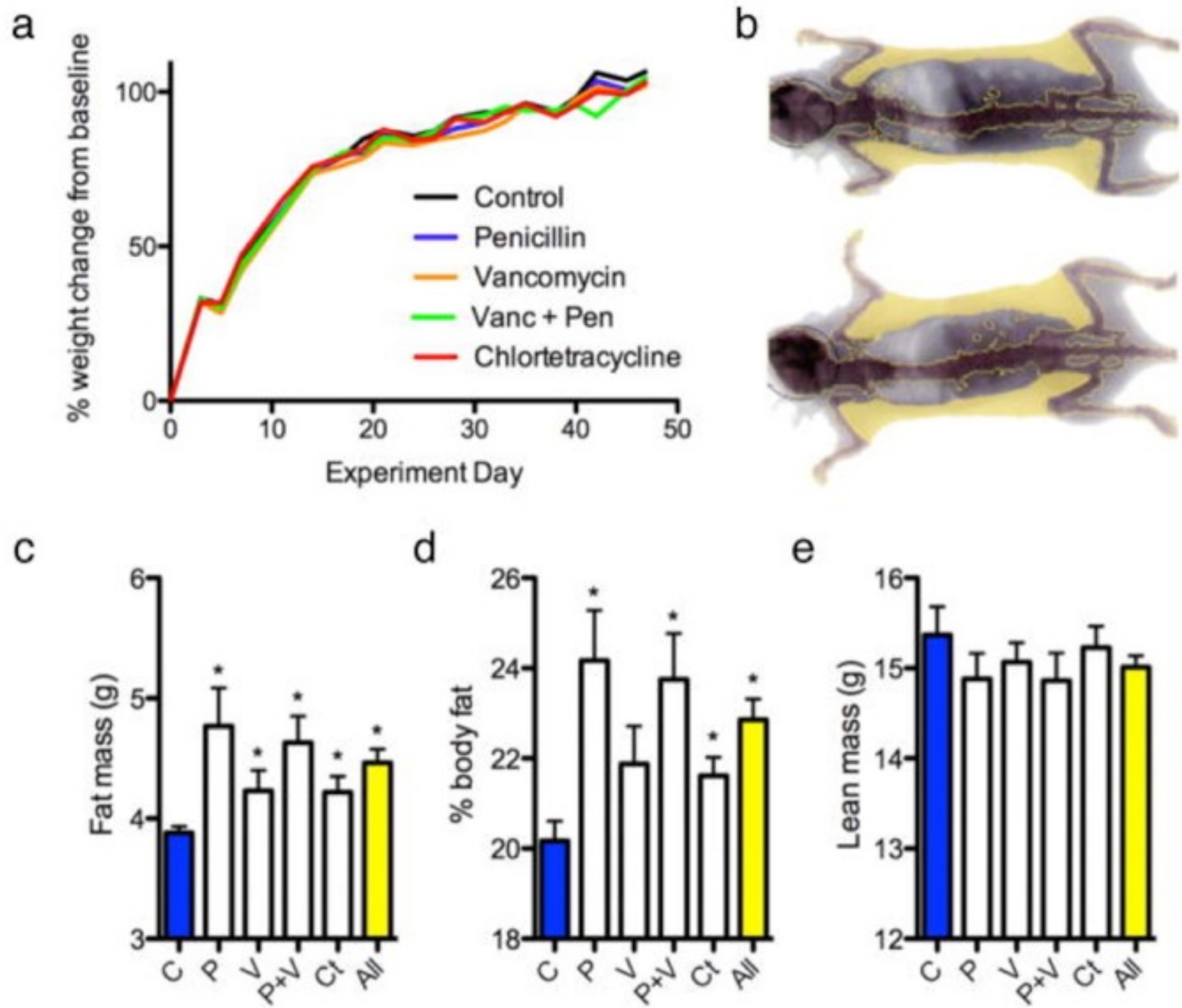


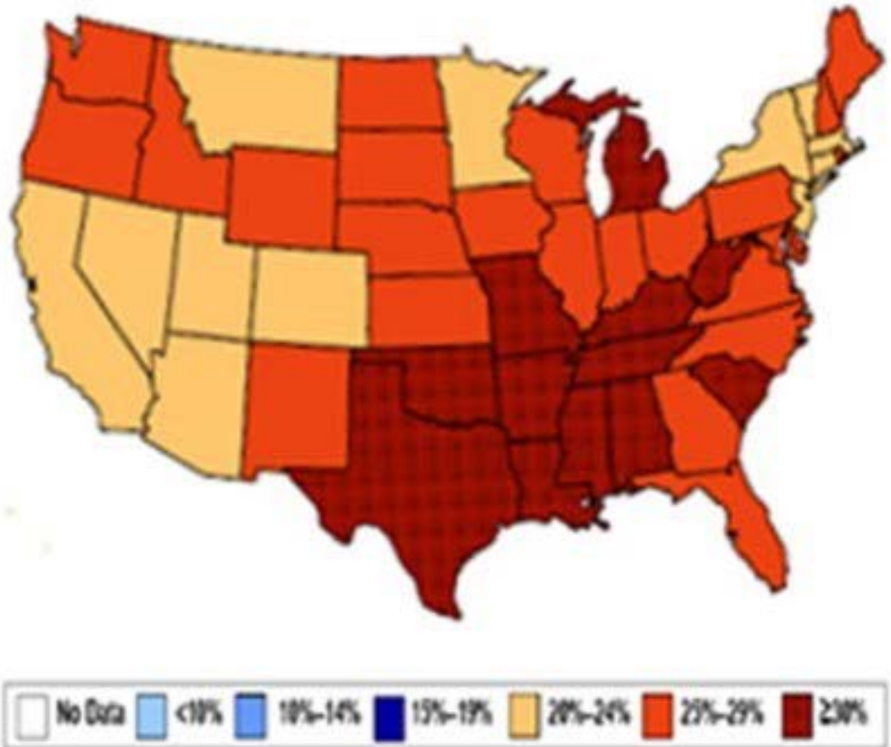


In *Missing Microbes*, Dr. Martin Blaser invites us into the wilds of the human microbiome where for hundreds of thousands of years bacterial and human cells have existed in a peaceful symbiosis that is responsible for the health and equilibrium of our body. Now, this invisible eden is being irrevocably damaged by some of our most revered medical advances—antibiotics—threatening the extinction of our irreplaceable microbes with terrible health consequences.

Antibiotics in Early Life Alter the Murine Colonic Microbiome and Adiposity

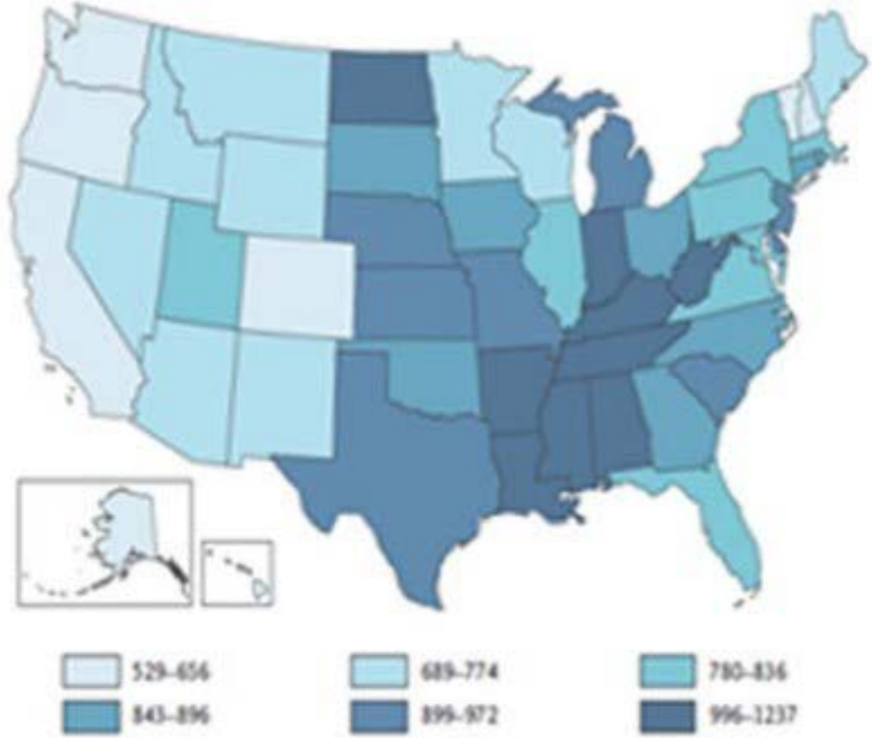
(Cho et al. Nature 2012)





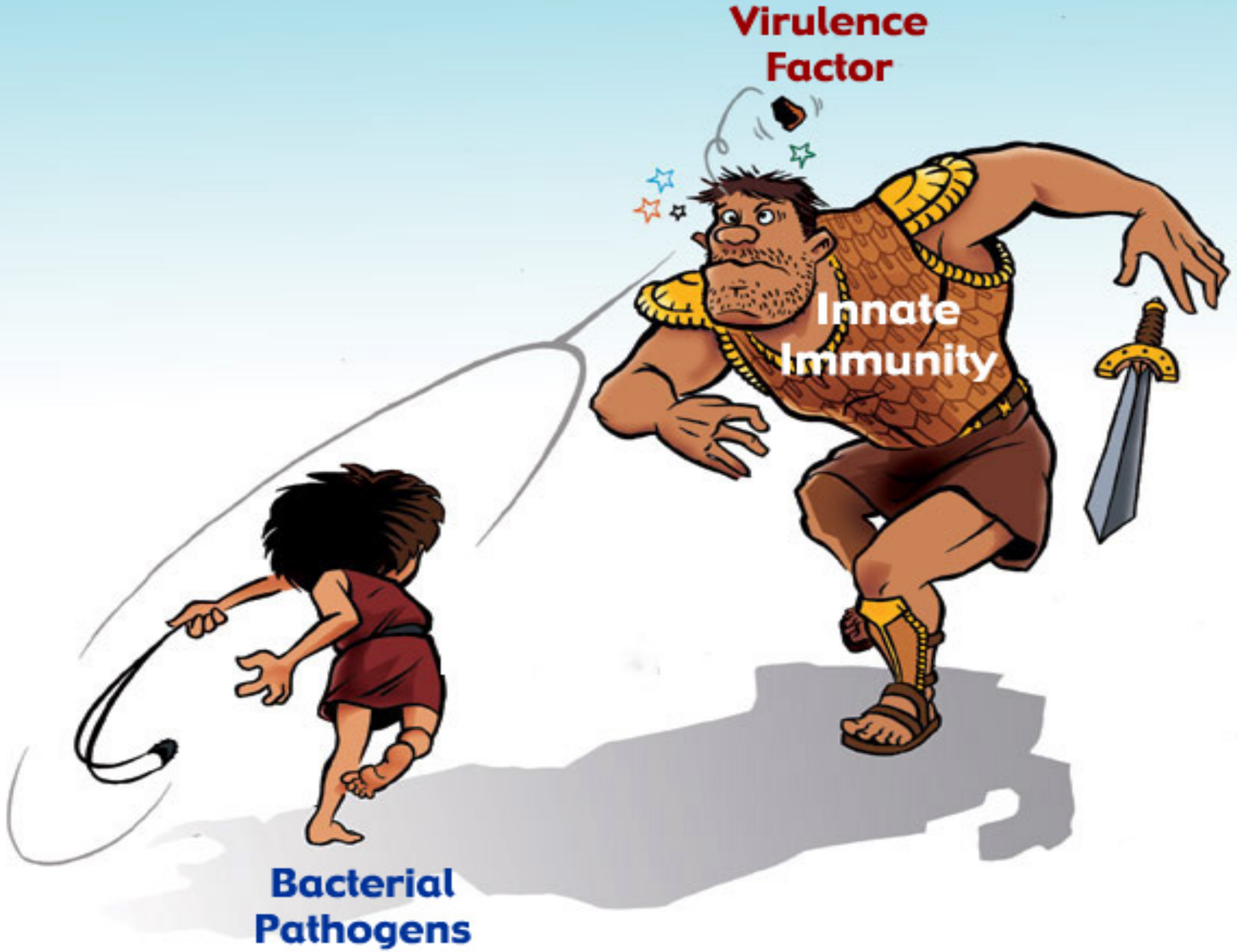
Obesity trends in US Adults, 2010

Source: CDC Behavioral Risk Factor Surveillance System.

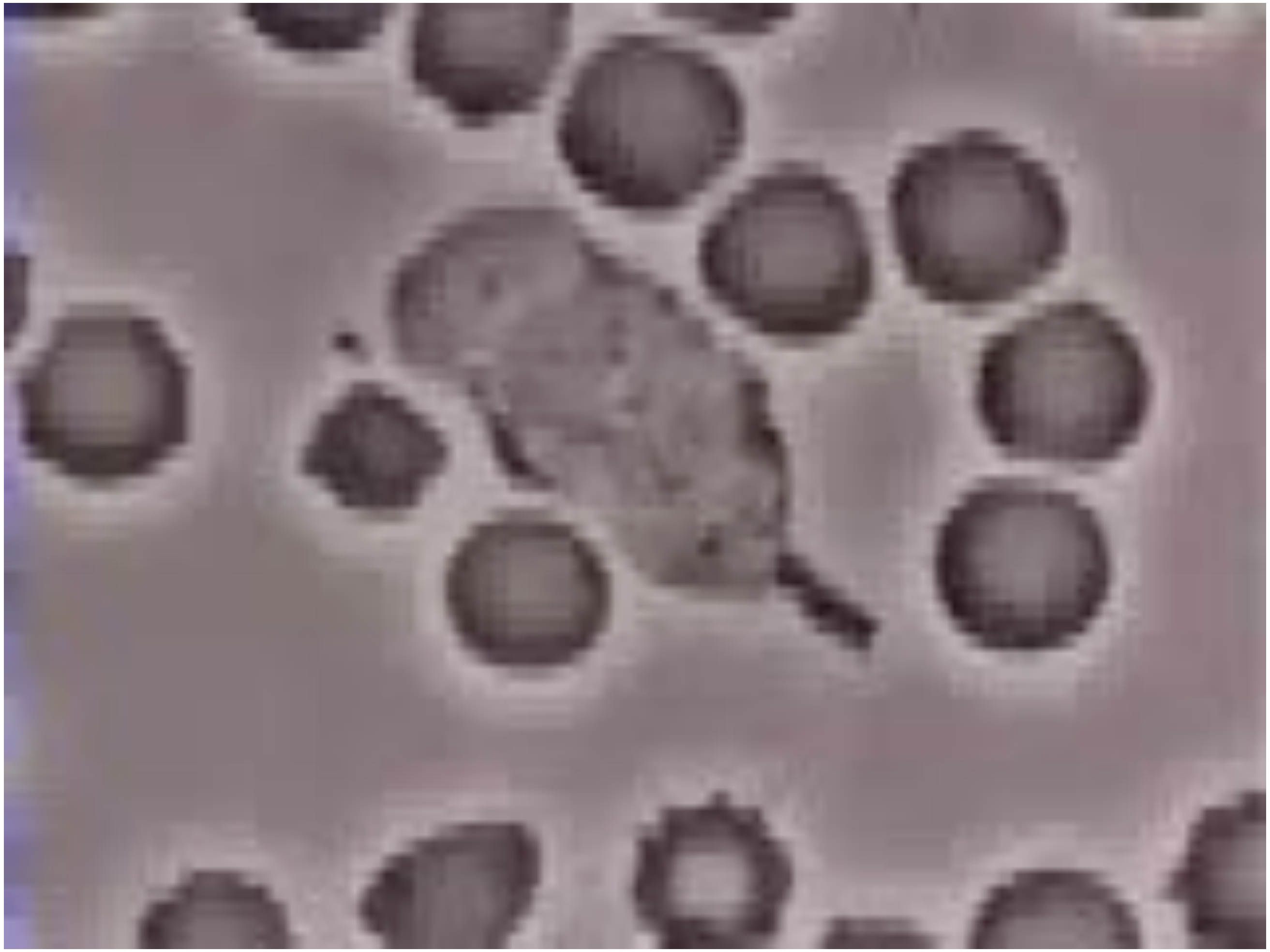


Antibiotic prescriptions per 1000 persons, 2010

Source: L Hicks, TH Taylor, RJ Hunkler. NEJM 2013, 368:1461.

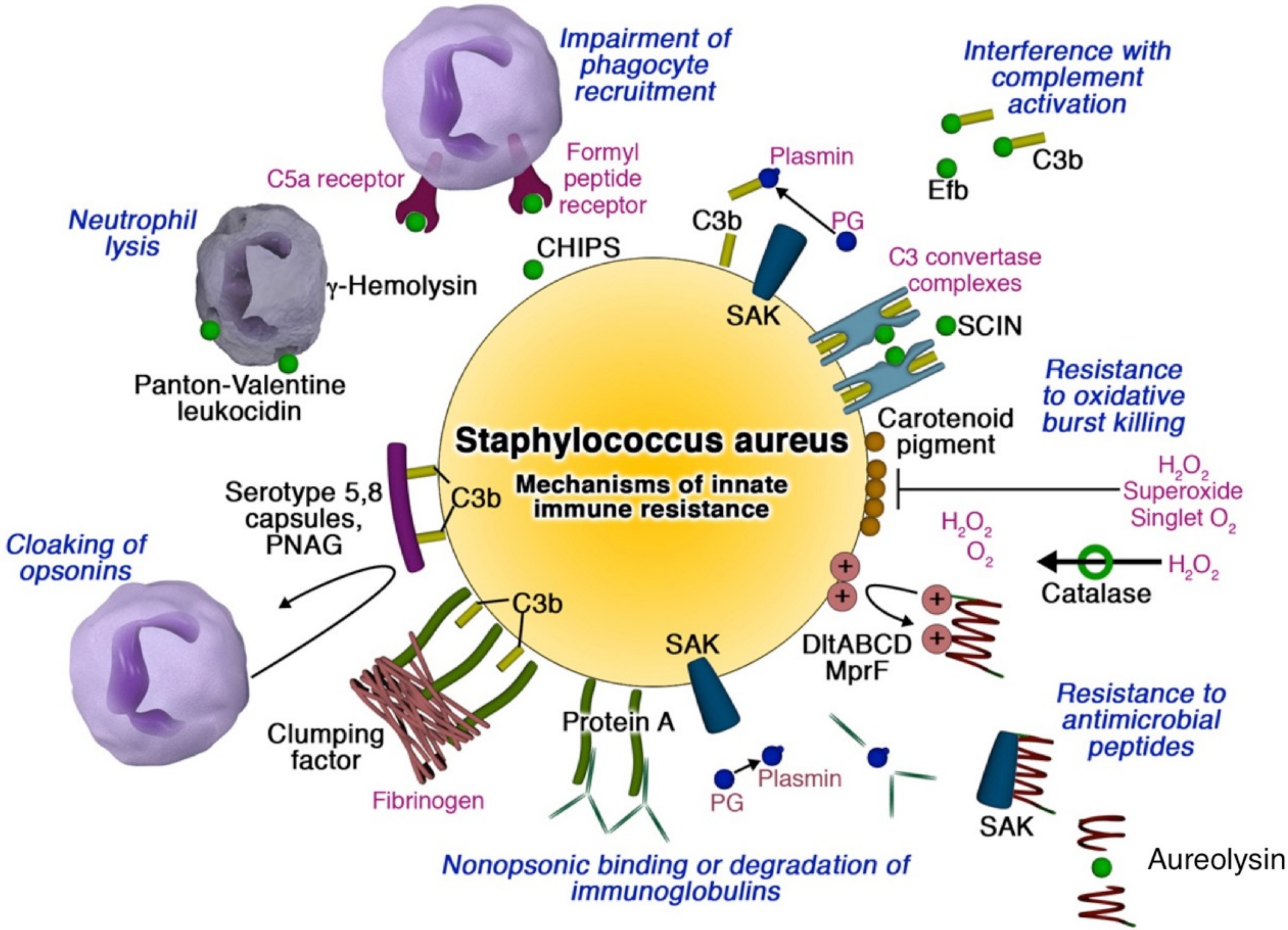

Virulence
Factor
Innate
Immunity
Bacterial
Pathogens

Human Neutrophil vs. Bacterial Pathogen



J. Sullivan “Cells Alive”

S. aureus Subversion of Host Phagocyte Defense



Nizet, J Allergy Clin Immunol 2007

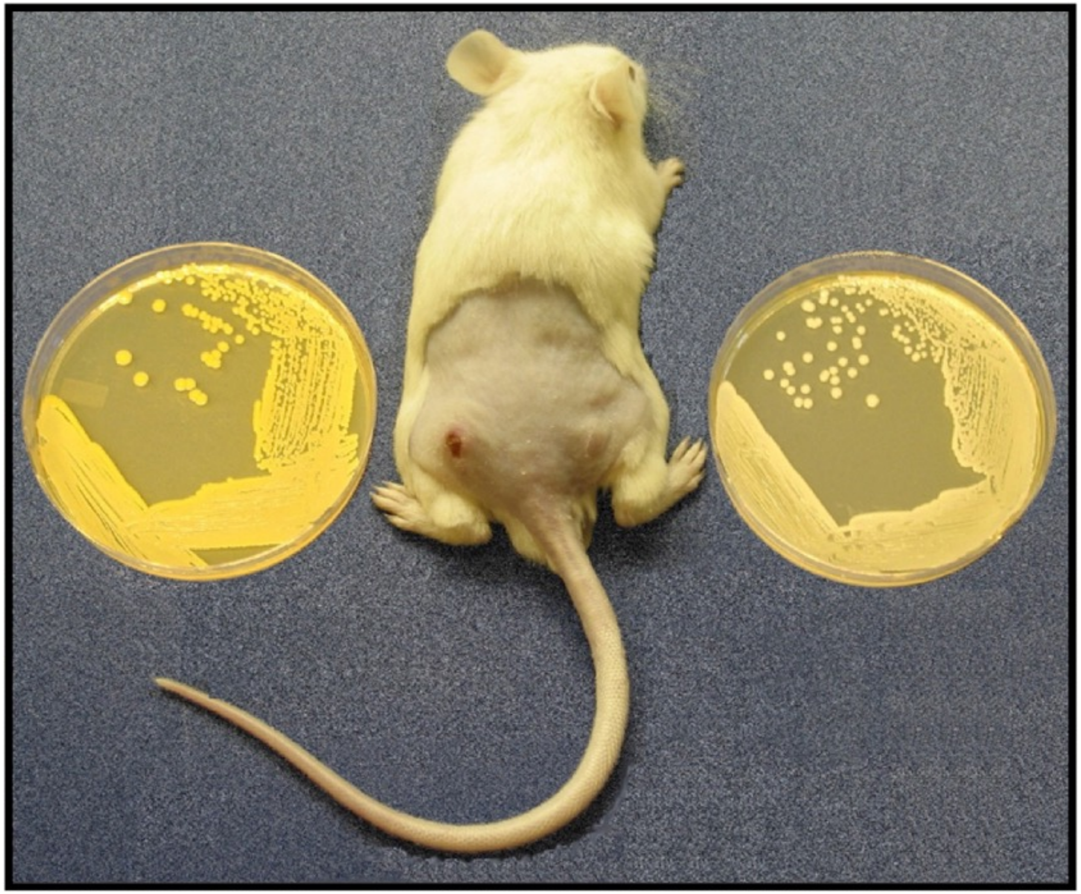
Seeking *alternatives* to classical antibiotics, especially very broad-spectrum agents, that kill bacteria or block their growth

* Drugs to block specific pathogen immune resistance factors
  - Sensitize pathogens to clearance by normal host innate defenses
  - More targeted therapy, avoid "collateral damage" to microbiome

* Modulation of innate immunity to treat bacterial infections
  - Can we pharmacologically boost phagocyte function?

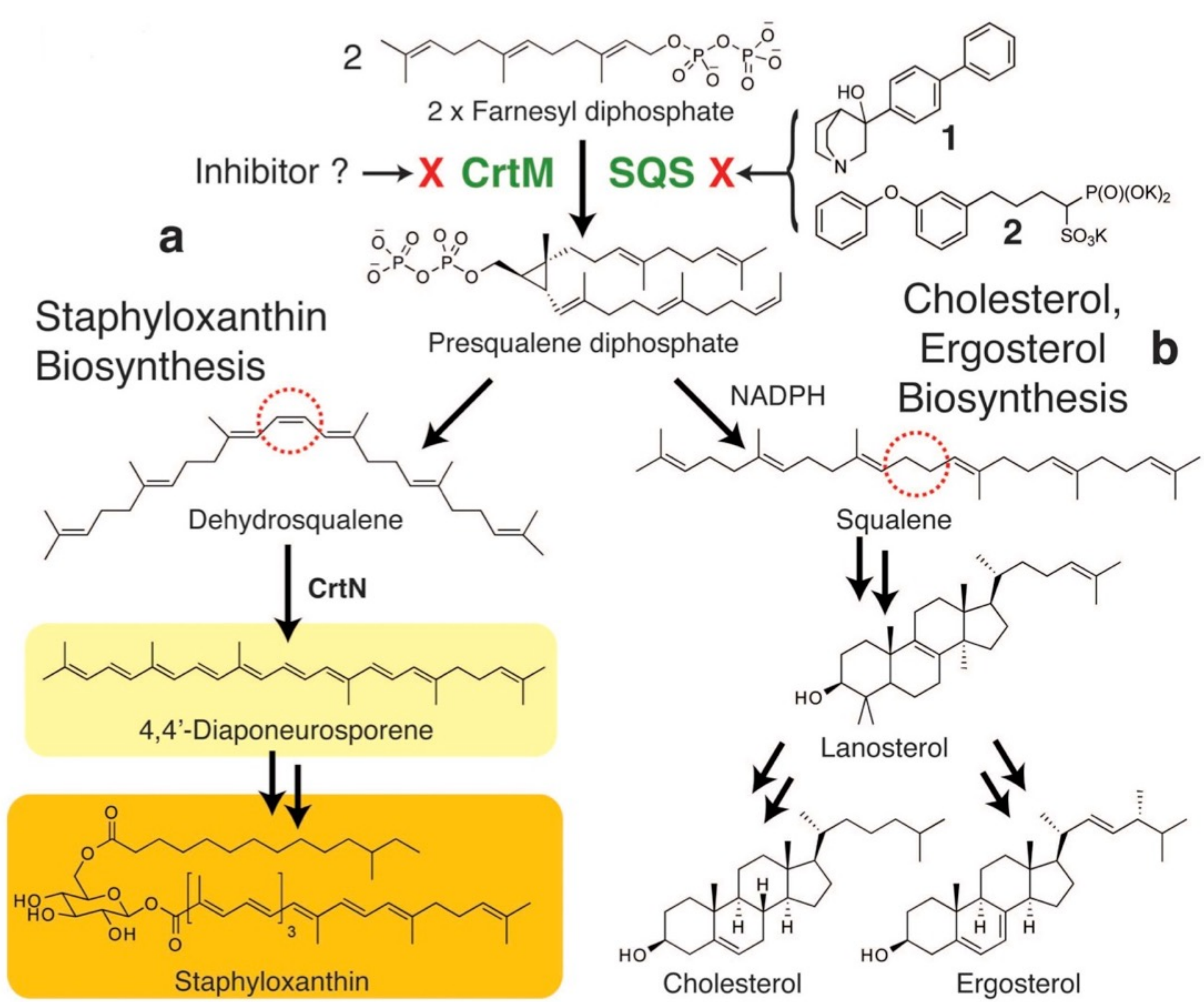
* Explore "repurposing" existing drugs for the above properties

* These approaches can work in concert with classical antibiotics



Target for therapy?

First Steps of Staphyloxanthin Biosynthesis Resemble Those of Human Cholesterol Biosynthesis



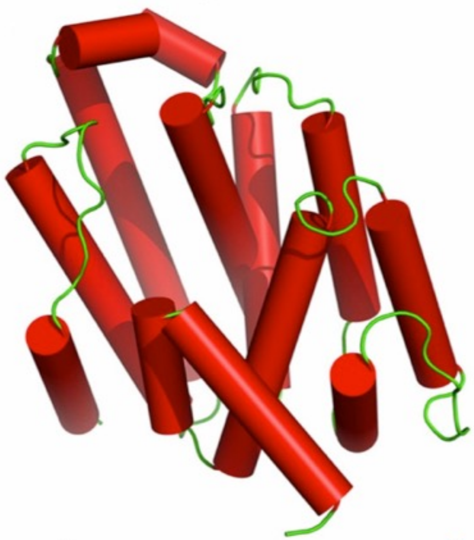
Liu et al. Science

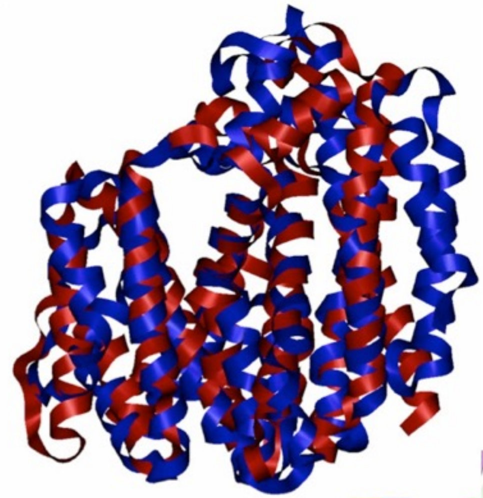
X-Ray Crystal Structures of *S. aureus* CrtM Together With Bound Phosphonosulfonate Inhibitors

Chia-I Liu
Wen-Ji Jeng
Andrew H.J. Wang

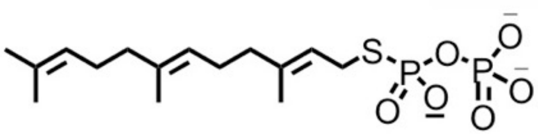
Academia Sinica
Taiwan

CrtM X-ray structure

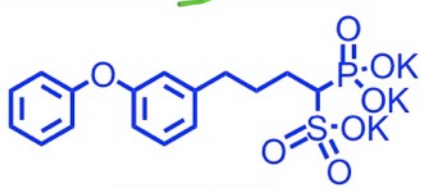




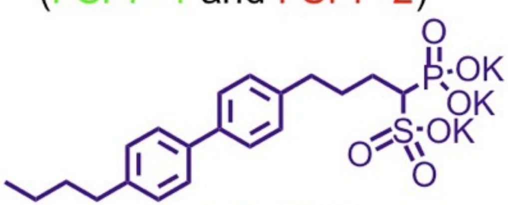
Superposition of CrtM and hSQS structures, showing a rmsd of 5.5 Å



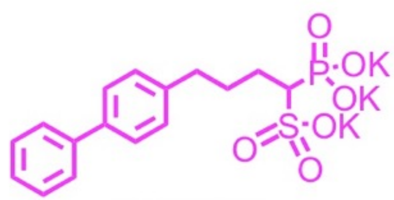
Farnesyl thiodiphosphate (FSPP-1 and FSPP-2)



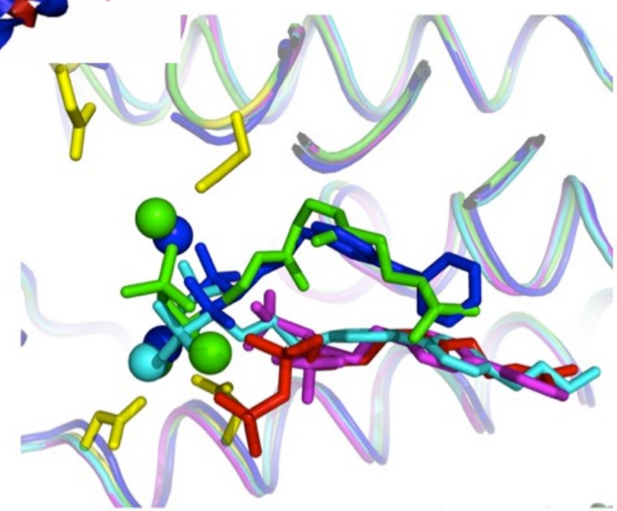
BPH-652



BPH-698

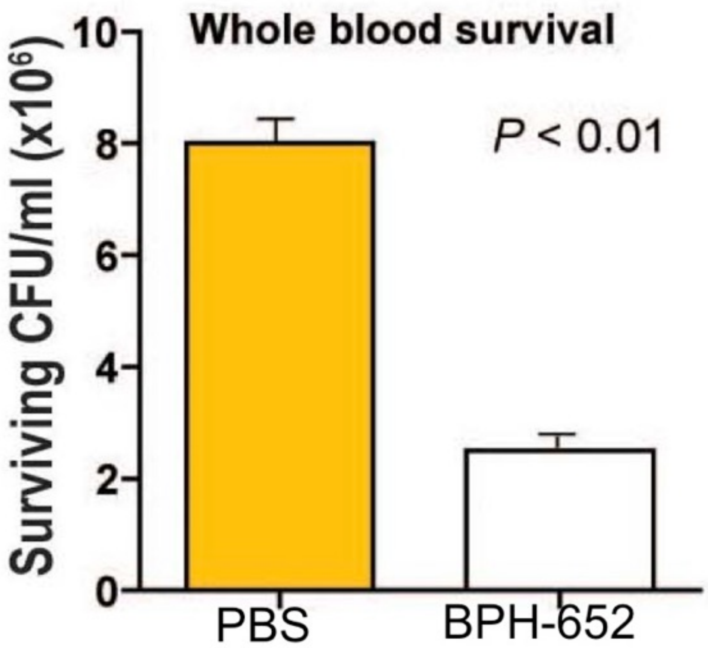


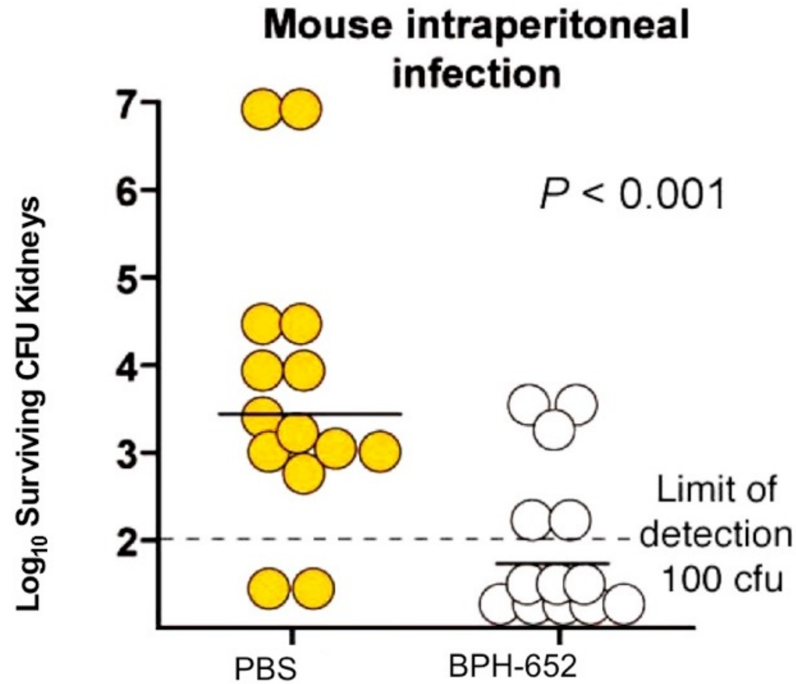
BPH-700



Liu et al. Science

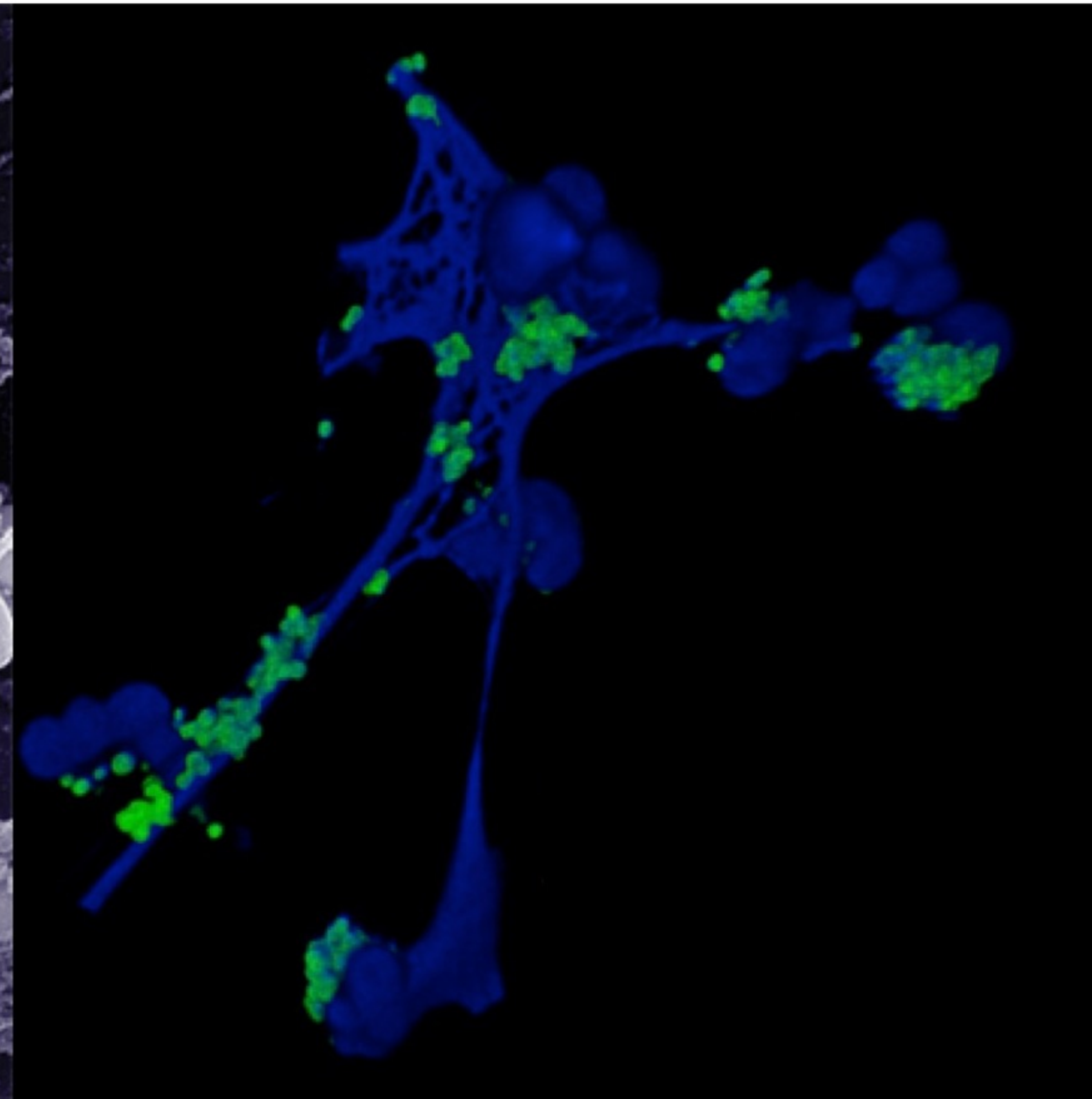
A Cholesterol-Lowering Agent Blocks *S. aureus* Virulence *In Vitro* & *In Vivo*





Liu et al. Science

Neutrophil “NETs”: DNA-Based Extracellular Traps for Killing Pathogenic Bacteria



Statins

> 40 million users in USA in 2015

3-Hydroxy 3-Methylglutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors

Pharmacological Effects

- ***Treatment of Hyperlipidemia***
- ***Lowers LDL***
- ***Raises HDL***

Clinical Data: Decreased Risk or Improved Outcomes of Infection in Patients Receiving Statins

Disease	Effect of Statins
Bacteremia	Reduced Mortality
Sepsis	Reduced Incidence, Reduced Mortality
Pneumonia	Reduced Incidence, Reduced Mortality

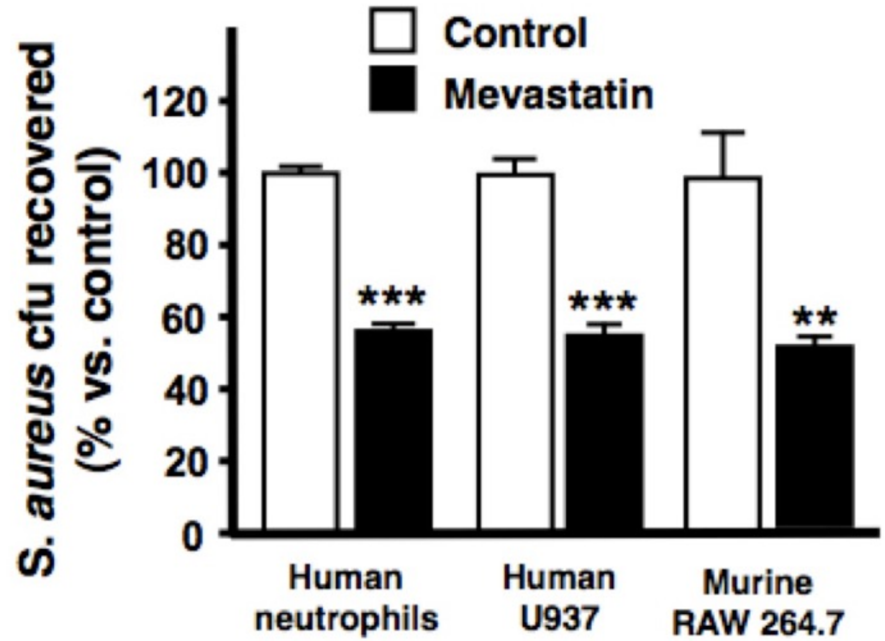
Prevailing Hypothesis: Statin downregulates inflammatory mediatory release deleterious in sepsis (TNF, iNOS, IL-1, IL-6)

We sought to test an Alternative Hypothesis:

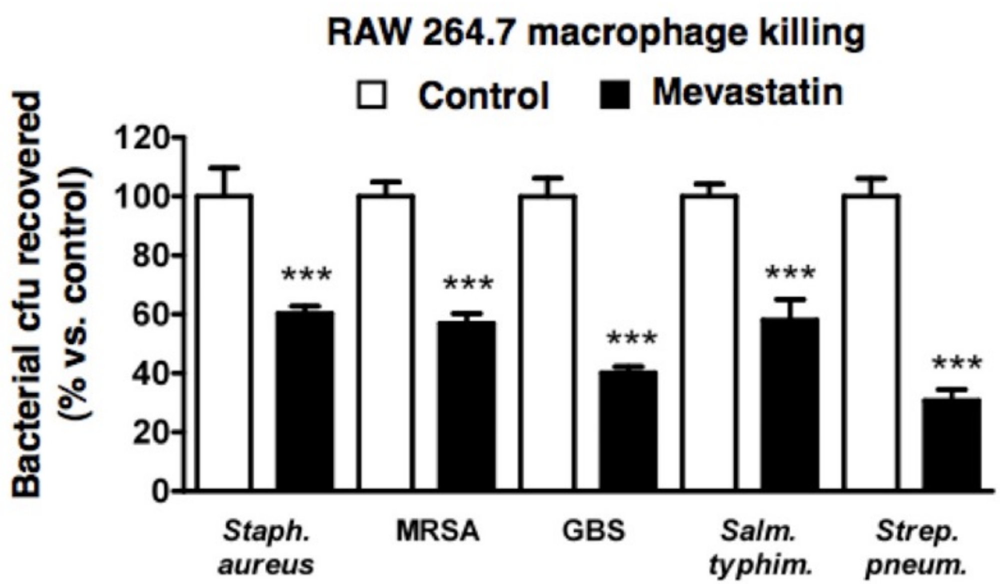
Could statins improves the innate immune function of phagocytes?

Statin treated neutrophils and macrophages kill *S. aureus* more efficiently

with
C. Glass Lab

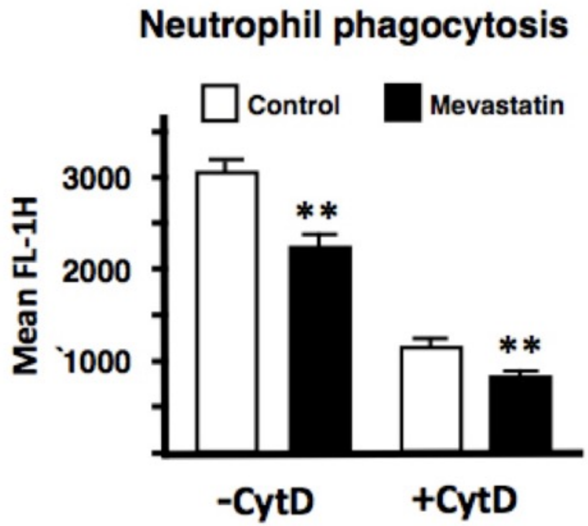


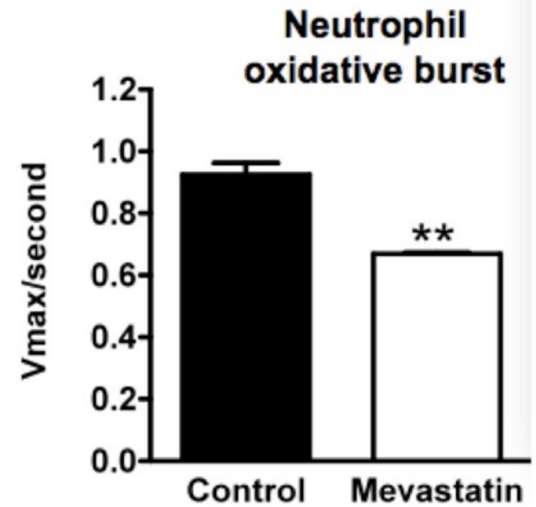
Effect is observed with multiple bacterial species

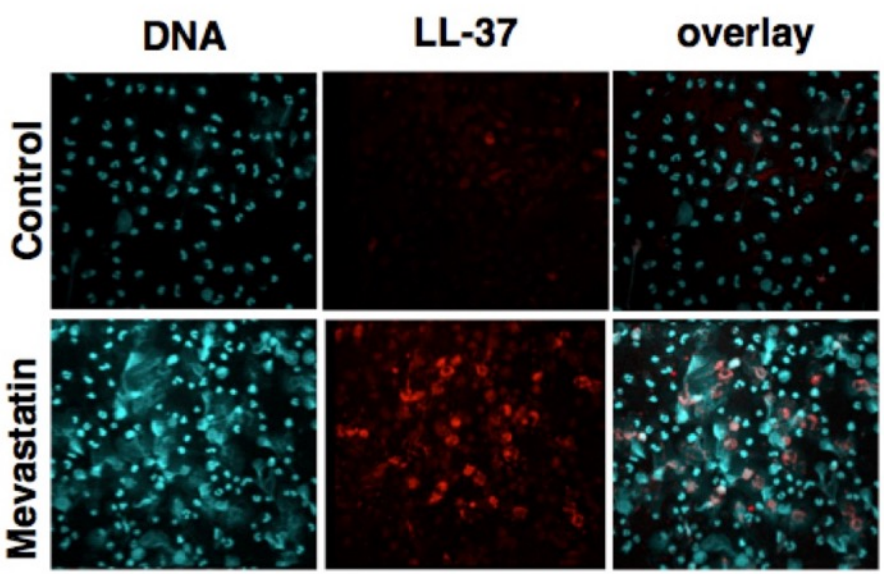


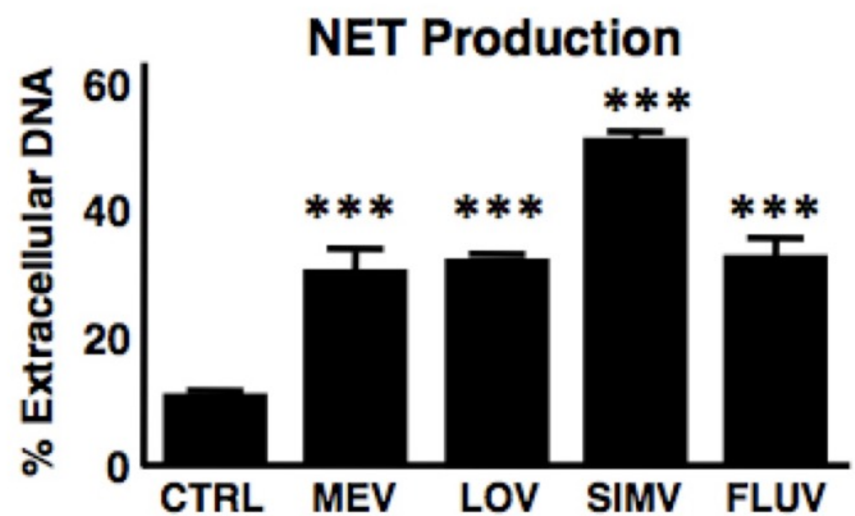
Chow et al. Cell Host Microbe (2010)

Statins actually REDUCED phagocytosis & oxidative burst; rather, they boosted NET production & killing



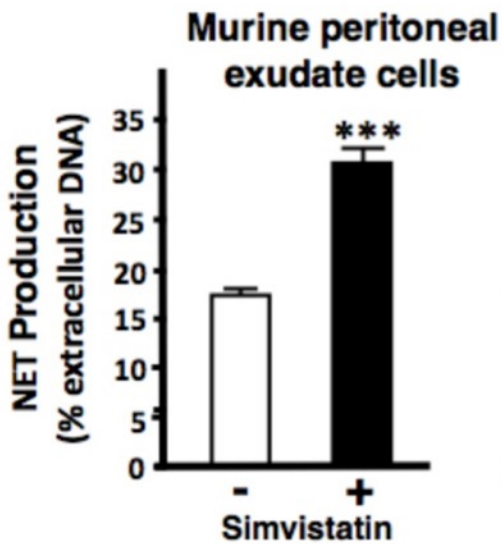


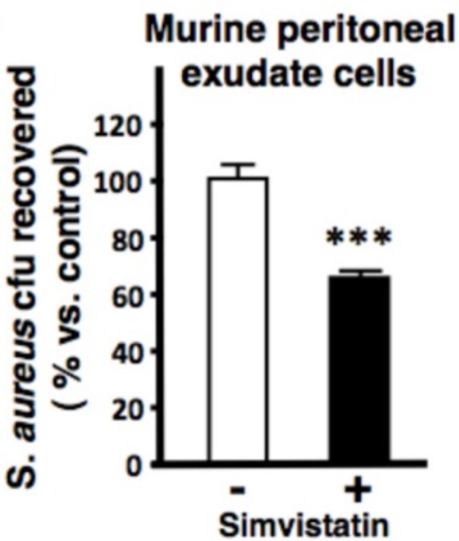


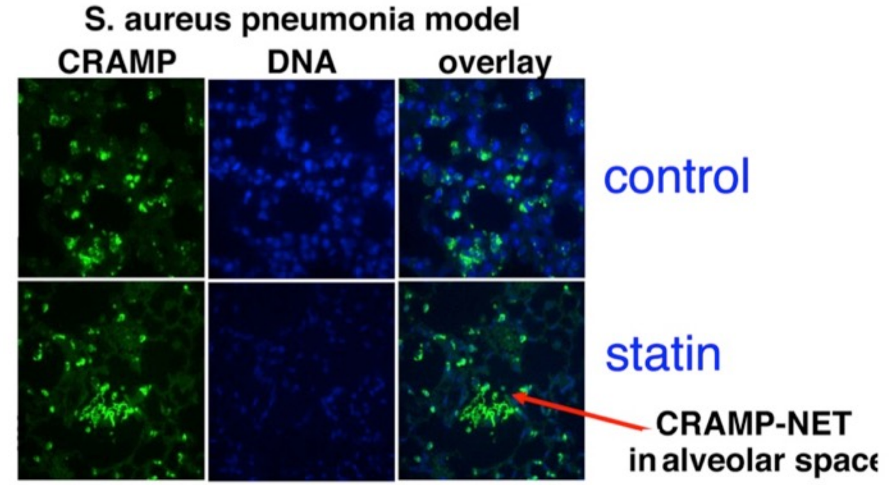


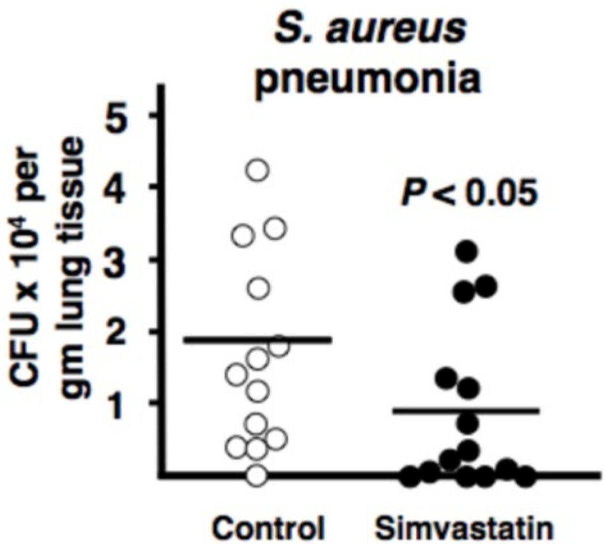
Chow et al. Cell Host Microbe (2010)

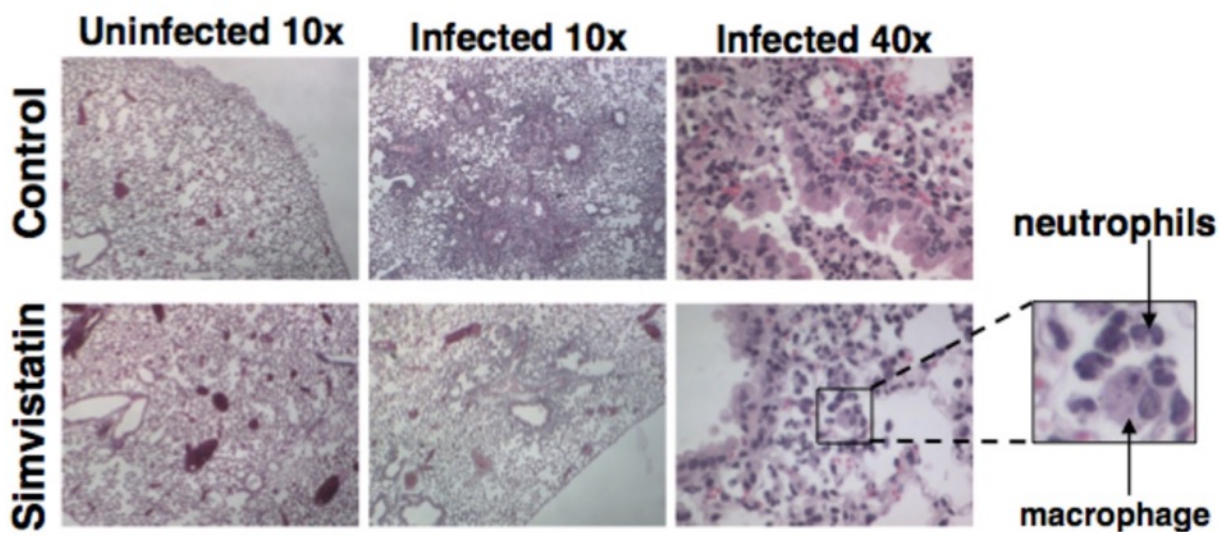
Mice Treated With Statin Have Increased ET Production and Killing of *S. aureus* Ex Vivo and In vivo





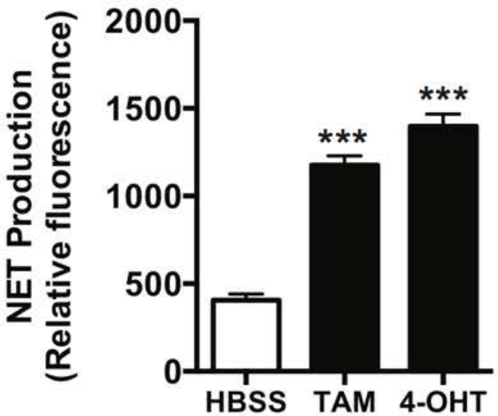


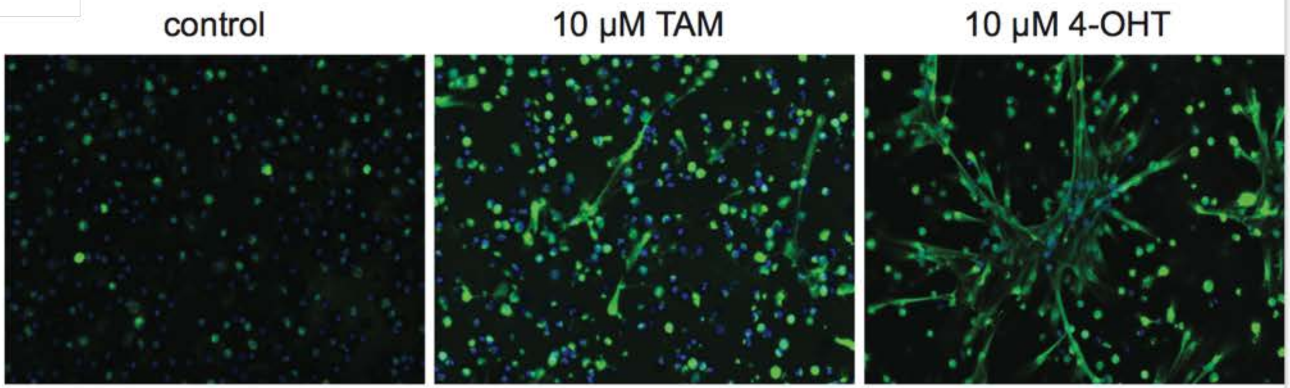


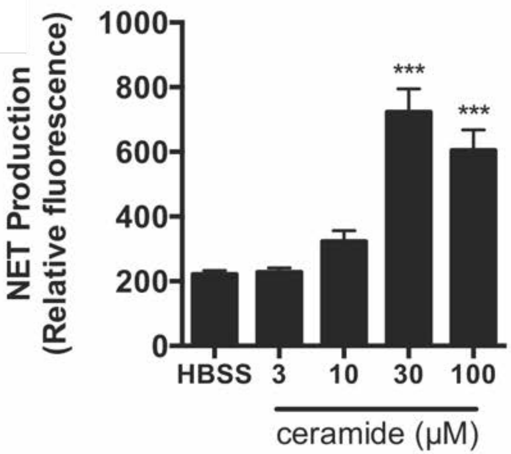


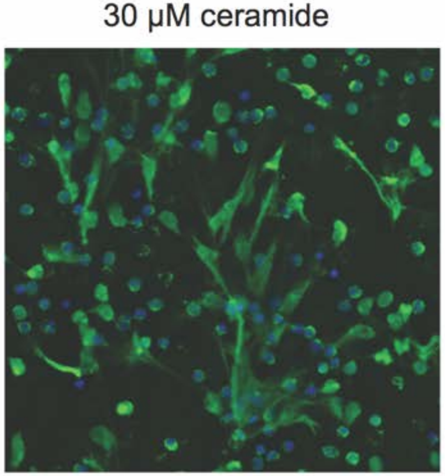
Chow et al. Cell Host Microbe (2010)

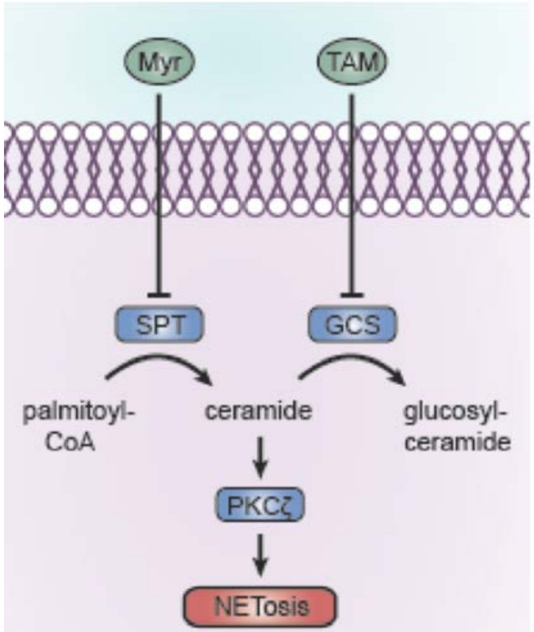
Tamoxifen Induces NETs By Increasing Intracellular Ceramide Levels





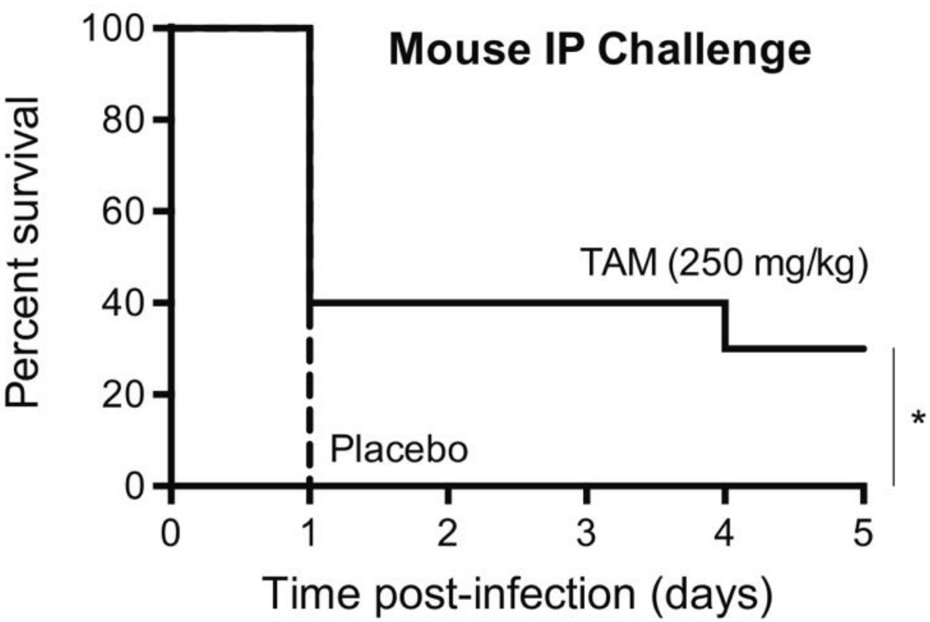


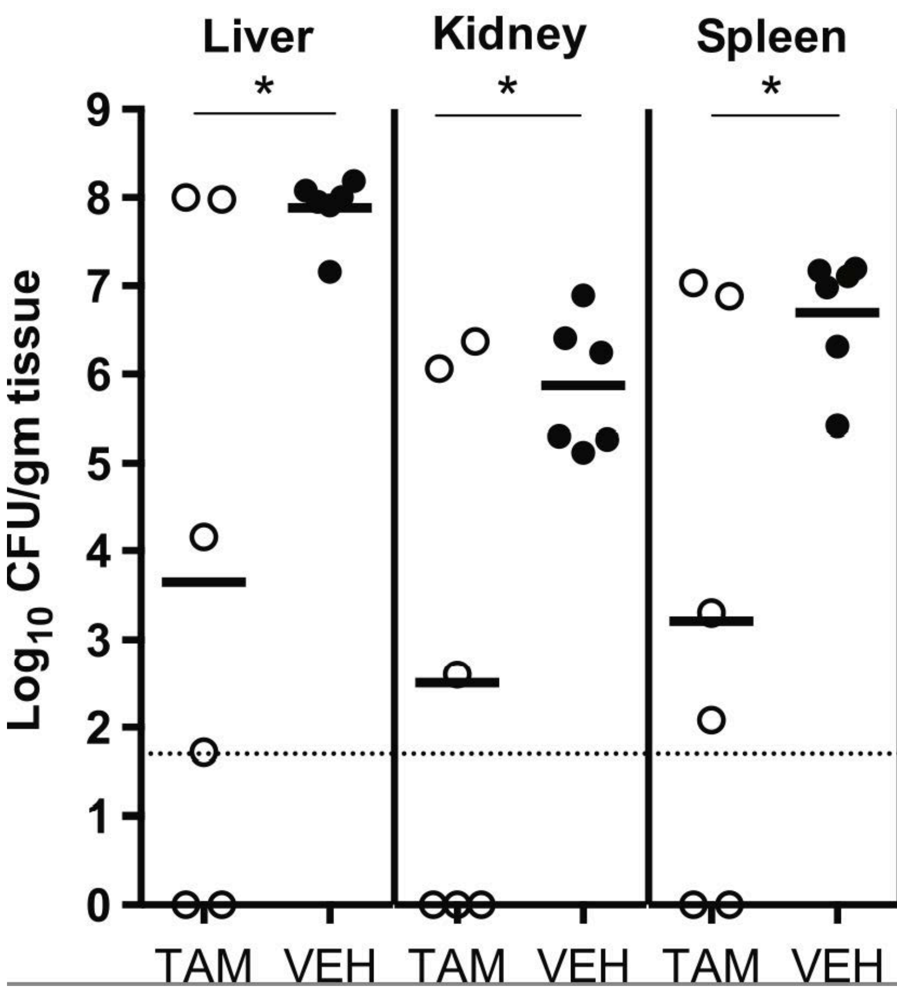




Corriden et al. Nat Commun 2015

Tamoxifen Boosts Host Defense Against Staphylococcal Infection in vivo





Corriden et al. Nat Commun 2015

Proc Soc Exp Biol Med, 48: 330-333 (1941)

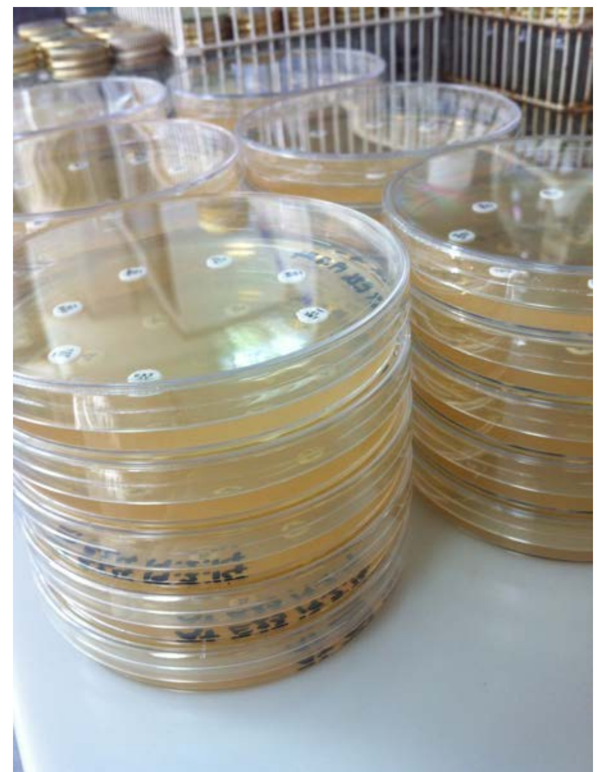
A Protein-Free Medium for Primary Isolation of the Gonococcus and Meningococcus.

J. HOWARD MUELLER AND JANE HINTON.

From the Department of Bacteriology and Immunology, Harvard Medical School, and School of Public Health, and the Boston Dispensary, Boston, Mass.*

30.0% Beef infusion
1.75% Casein hydrosylate
0.15% Starch
1.70% Agar
pH to neutral at 25^{o}C

Later – cation-adjusted (for *Pseudomonas*)
Calcium 20-25 mg/L
Magnesium 10-12.5 mg/L

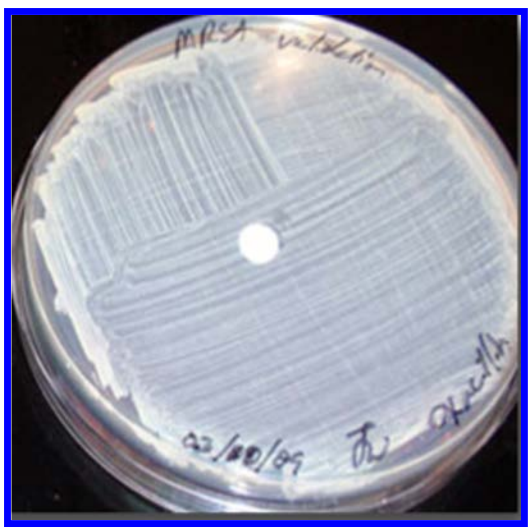


A SINGLE TEST, MIC/MBC TESTING IN BACTERIOLOGIC MEDIA (i.e. CA-MHB), ***EFFECTIVELY DELIMITS PHARMACOTHERAPY OF HUMAN BACTERIAL INFECTIONS***

ANTIBIOTIC DISCOVERY AND DEVELOPMENT

WHICH DRUGS CHOSEN FOR HOSPITAL FORMULARY

WHICH INFORMATION IS PROVIDED TO DOCTORS WHEN THE PATHOGEN IS CULTURED FROM THE PATIENT



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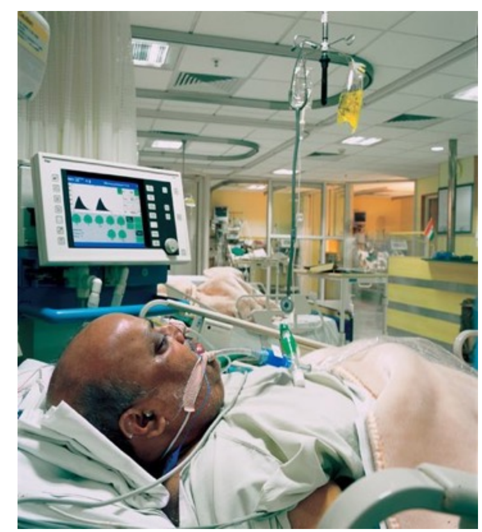
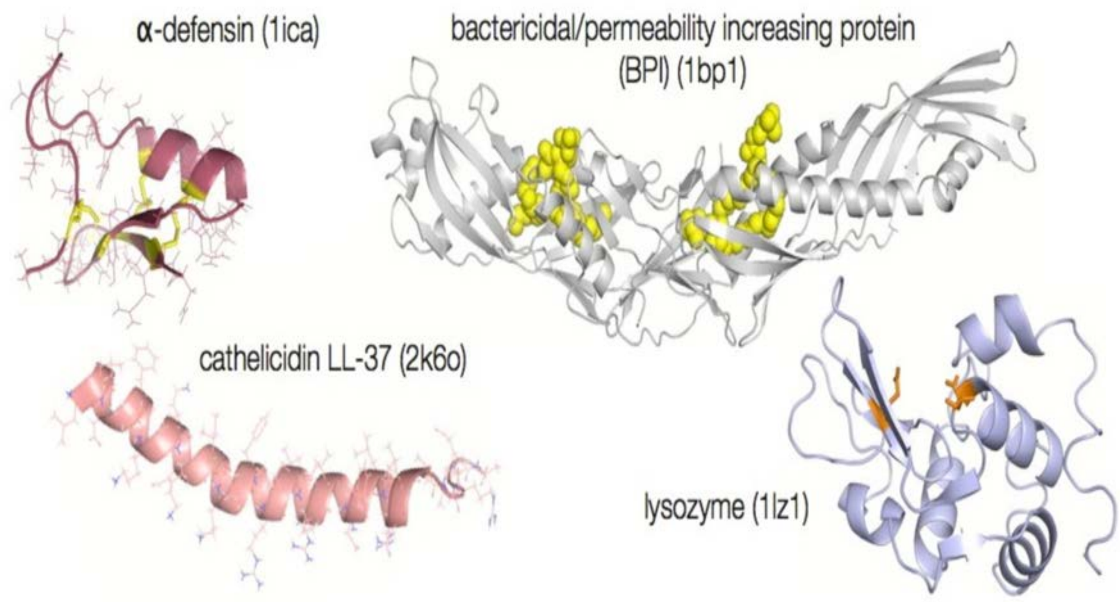


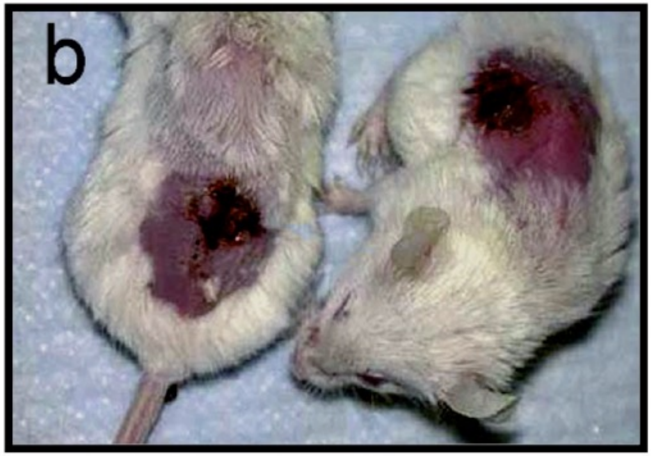
Before a patient has even seen the doctor ...

... their infection is already being treated by dozens of antibiotics

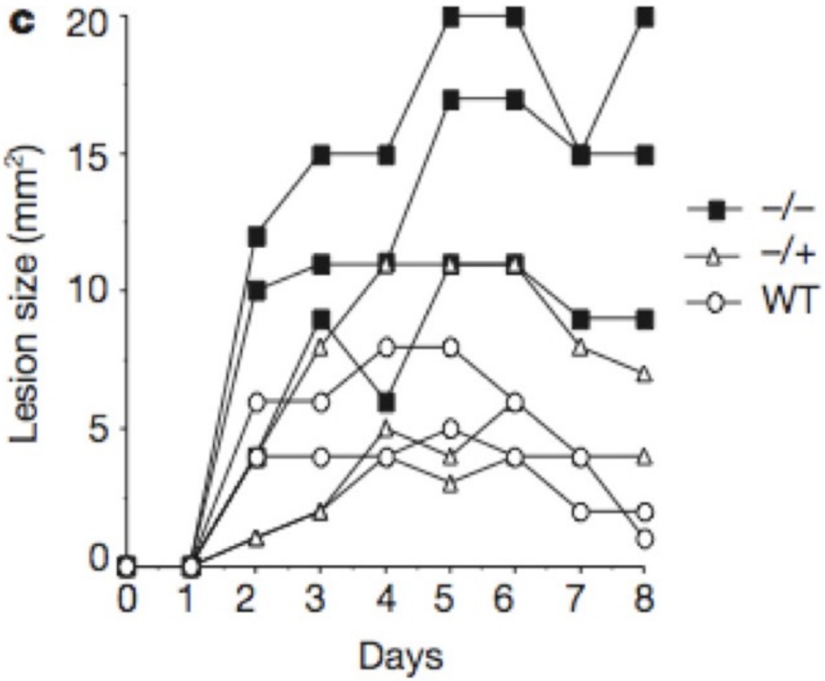


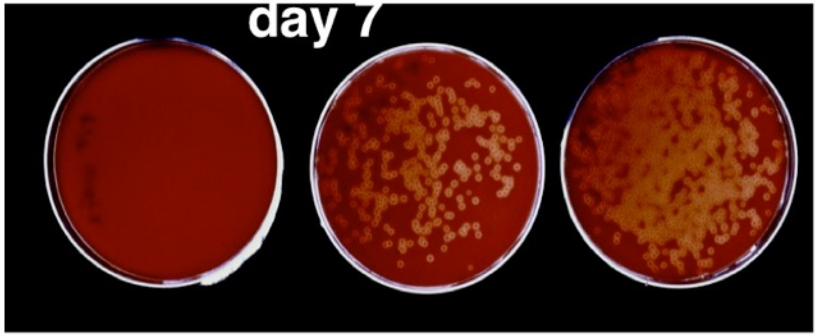
CRAMP-KO Mouse Has Immune Defect

Wild-type Mice



Knockout Mice





+/+ +/- -/-

with R. Gallo Lab

Nizet *et al.* Nature, 2001

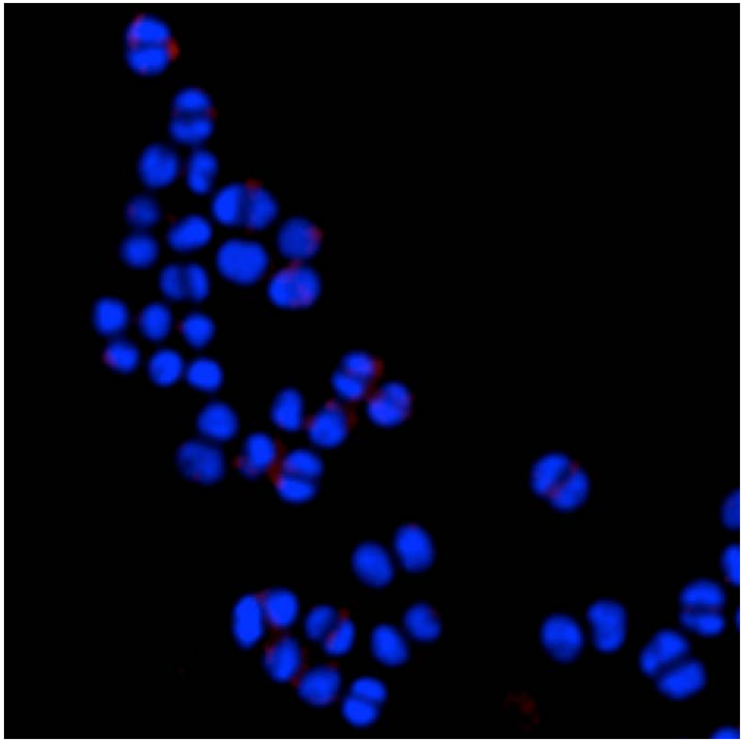
Reintroduction of β-Lactam Antibiotics in Refractory M.R.S.A. Bacteremia – With Surprising Results

Day 1	Day 12	Day 17	Day 21	Day 22	Day 23-76
VAN MIC 1 DAP MIC 0.5 (isolate D592)	Persistent (+) blood cultures for MRSA →		VAN MIC 4.0 DAP MIC 2.0 (isolate D712)	Bacteremia Resolved	Cure
Vancomycin dosed for serum trough 15-20 mg/L	Daptomycin 6 mg/kg	Daptomycin 8 mg/kg + Gentamicin	Daptomycin 10 mg/kg **+ Nafcillin 2 g IV q 4hr**		

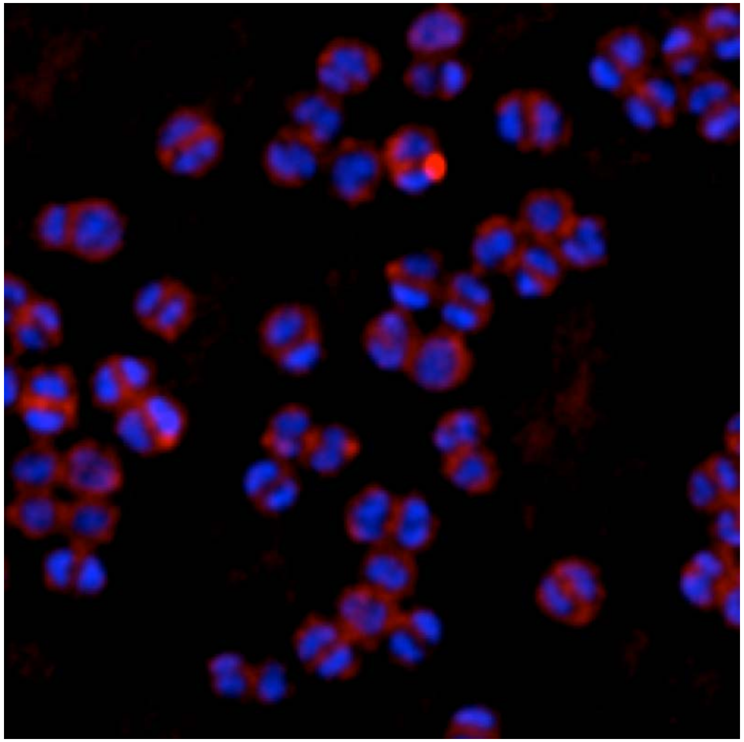
George Sakoulas, MD

Sakoulas et al. J Mol Med 2014

Nafcillin Increases Binding to MRSA by Rhodamine-Labeled Cathelicidin LL-37



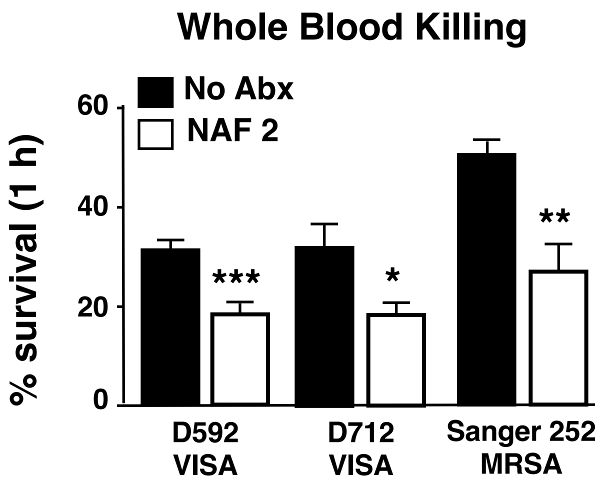
MRSA + LL-37

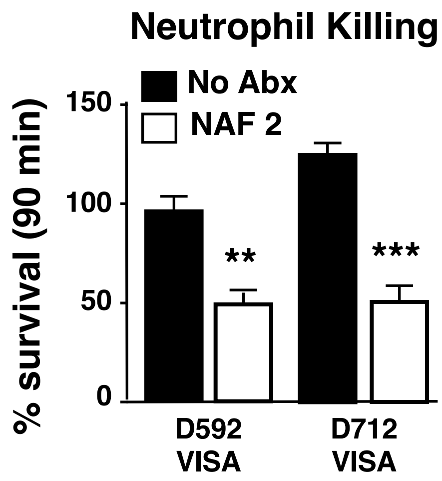


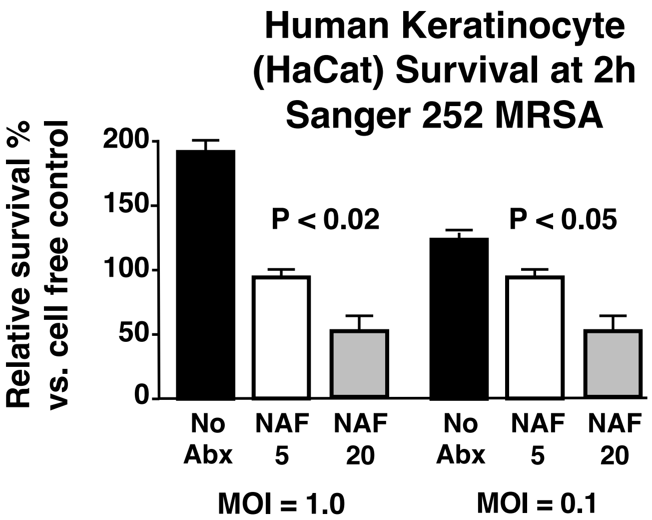
MRSA + LL-37
+ Naf 10

Sakoulas et al. J Mol Med 2014

Sublethal Nafcillin Sensitizes MRSA/VISA Strains to Whole Blood, Neutrophil & Keratinocyte Killing



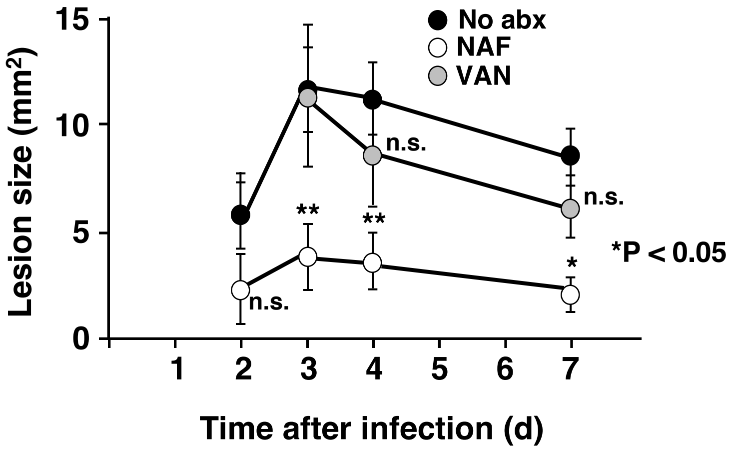




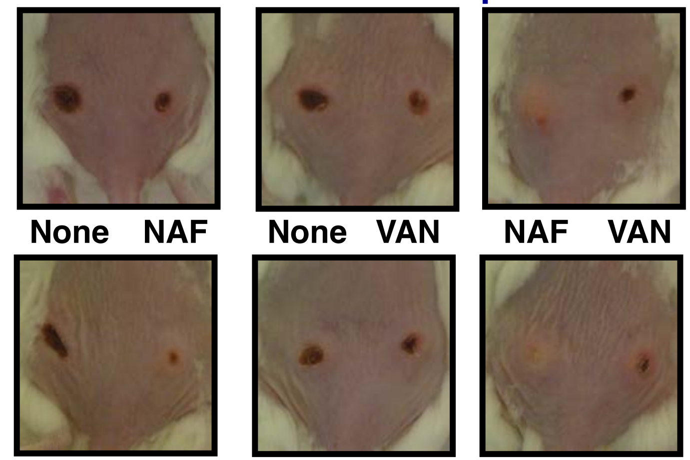
Sakoulas et al. J Mol Med 2014

Sublethal Nafcillin (Monotherapy) Influences MRSA Lesion Development in Mouse Skin Infection Models

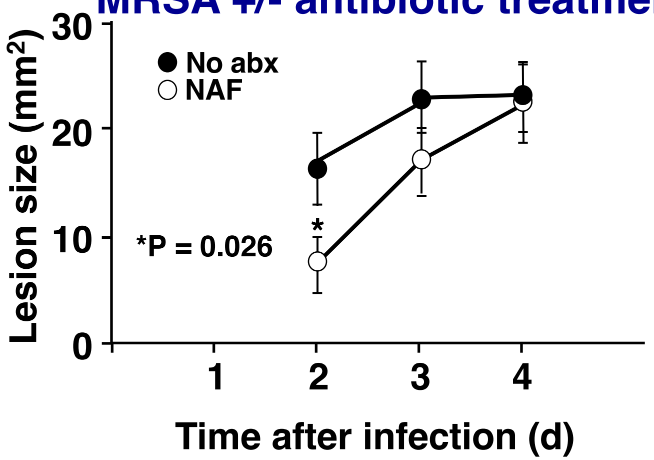
Antibiotic pretreatment of Sanger 252 MRSA followed by mouse subcutaneous challenge



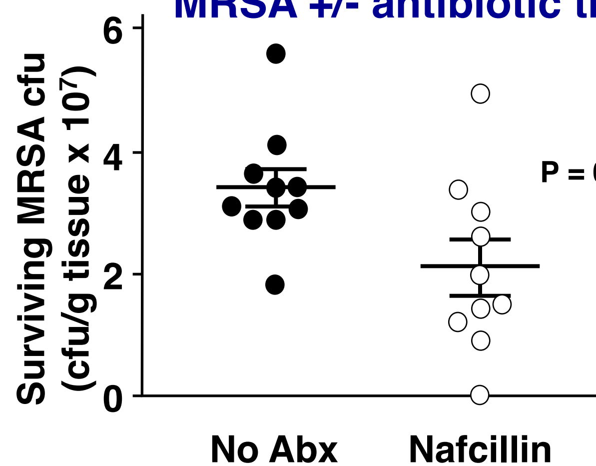
Representative gross appearance of skin lesions at 48 h time point



Mouse s.c. challenge with Sanger 252 MRSA +/- antibiotic treatment



Mouse s.c. challenge with Sanger 252 MRSA +/- antibiotic treatment



Sakoulas et al. J Mol Med 2014

THREAT LEVEL **URGENT**

This bacteria is an immediate public health threat that requires urgent and aggressive action.

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

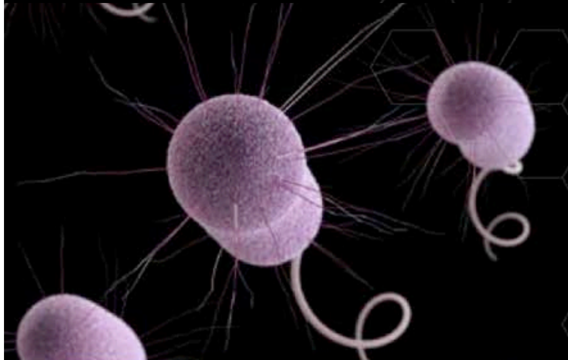
9,000 DRUG-RESISTANT INFECTIONS PER YEAR

600 DEATHS

CARBAPENEM-RESISTANT *KLEBSIELLA SPP.* **7,900**

1,400 CARBAPENEM-RESISTANT *E. COLI*

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS



THREAT LEVEL **SERIOUS**

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

MULTIDRUG-RESISTANT PSEUDOMONAS AERUGINOSA

6,700 MULTIDRUG-RESISTANT *PSEUDOMONAS* INFECTIONS

440 DEATHS

51,000 *PSEUDOMONAS* INFECTIONS PER YEAR

THREAT LEVEL **SERIOUS**

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

MULTIDRUG-RESISTANT ACINETOBACTER

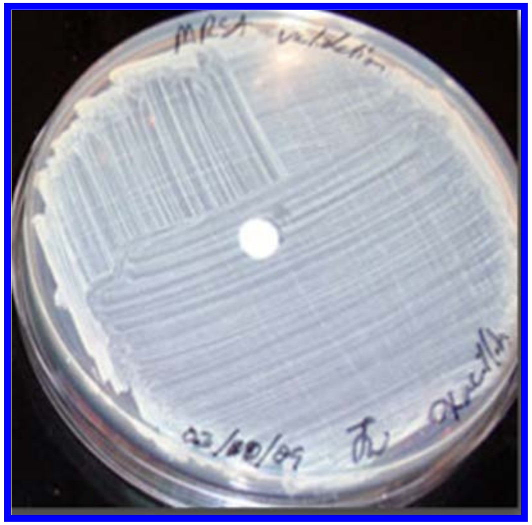
7,300 MULTIDRUG-RESISTANT *ACINETOBACTER* INFECTIONS

500 DEATHS FROM MULTIDRUG-RESISTANT INFECTIONS

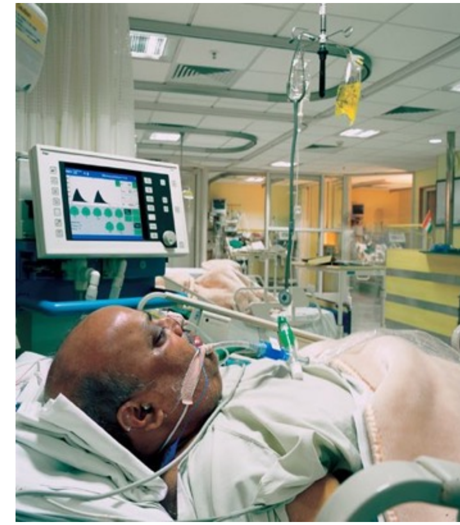
12,000 *ACINETOBACTER* INFECTIONS PER YEAR

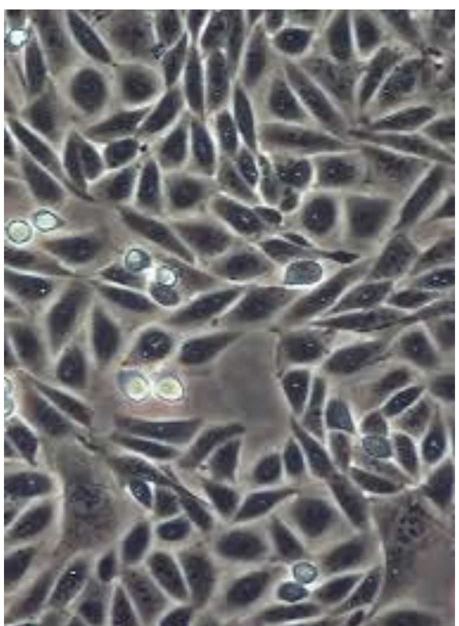
AT LEAST THREE DIFFERENT CLASSES OF ANTIBIOTICS **NO LONGER CURE RESISTANT ACINETOBACTER INFECTIONS**

ANTIBIOTIC	*Pseudomonas aeruginosa*, P4 (MDR)		*Klebsiella pneumoniae*, K1100 (MDR, KPC)		*Acinetobacter baumannii*, AB5075 (MDR)	
	MIC	Interpretation	MIC	Interpretation	MIC	Interpretation
Ampicillin	≥ 32	R	≥ 32	R	≥ 32	R
Amoxicillin/Clavulanate	≥ 32	R	≥ 32	R	≥ 32	R
Ampicillin/Sulbactam	≥ 32	R	≥ 32	R	≥ 32	R
Ticarcillin			≥ 128	R	≥ 128	R
Ticarcillin/Clavulanate	≥ 128	R				
Pipericillin	≥ 128	R	≥ 128	R	≥ 128	R
Pipericillin/Tazobactam	≥ 128	R	≥ 128	R	≥ 128	R
Cefalotin	≥ 64	R	≥ 64	R	≥ 64	R
Cefazolin	≥ 64	R	≥ 64	R	≥ 64	R
Cefuroxime	≥ 64	R	≥ 64	R	≥ 64	R
Cefuroxime Axetil	≥ 64	R	≥ 64	R	≥ 64	R
Cefotetan	≥ 64	R	8	*R	≥ 64	R
Cefoxitin	≥ 64	R	32	R	≥ 64	R
Cefpodoxime	≥ 8	R	≥ 8	R	≥ 8	R
Cefotaxime	≥ 64	R	8	R	≥ 64	R
Ceftazidime	≥ 64	R	≥ 64	R	≥ 64	R
Ceftizoxime	≥ 64	R	4	*R	≥ 64	R
Ceftriaxone	≥ 64	R	≥ 64	R	≥ 64	R
Cefepime	≥ 64	R	4	*R	≥ 64	R
Aztreonam	≥ 64	R	≥ 64	R	≥ 64	R
Doripenem	≥ 8	R	≥ 8	R	≥ 8	
Ertapenem			≥ 8	R		
Imipenem	≥ 16	R	8	R	≥ 16	R
Meropenem	≥ 16	R	≥ 16	R	≥ 16	R
Amikacin	32	I	≥ 64	R	≥ 64	R
Gentamicin	8	I	≥ 16	R	≥ 16	R
Tobramycin	≤ 1	S	≥ 16	R	8	I
Nalidixic Acid	≥ 32	R	≥ 32	R	≥ 32	R
Ciprofloxacin	≥ 4	R	≥ 4	R	≥ 4	R
Levofloxacin	≥ 8	R	≥ 8	R	4	I
Moxifloxacin	≥ 8	R	≥ 8	R	≥ 8	R
Norfloxacin	8	I	≥ 16	R	≥ 16	R
Tetracycline	≥ 16	R	4	S	≤ 1	S
Tigecycline	≥ 8	R	4	I	≤ 0.5	S
Nitrofurantoin	≥ 512	R	128	R	≥ 512	R
TMP/SFX	≥ 320	R	40	S	≥ 320	R




dreamstime.com






RPMI-1640
0.2 um Filtered
Contains: L-Glutamine
Catalog #: 30041
Lot #: E067-6
Volume: 500 mL Exp. Date: 06/07

Dramatic Differences in Azithromycin Activity vs. Multidrug-Resistant Gram-Negative Rods in Tissue Culture Media vs. Bacteriologic Media

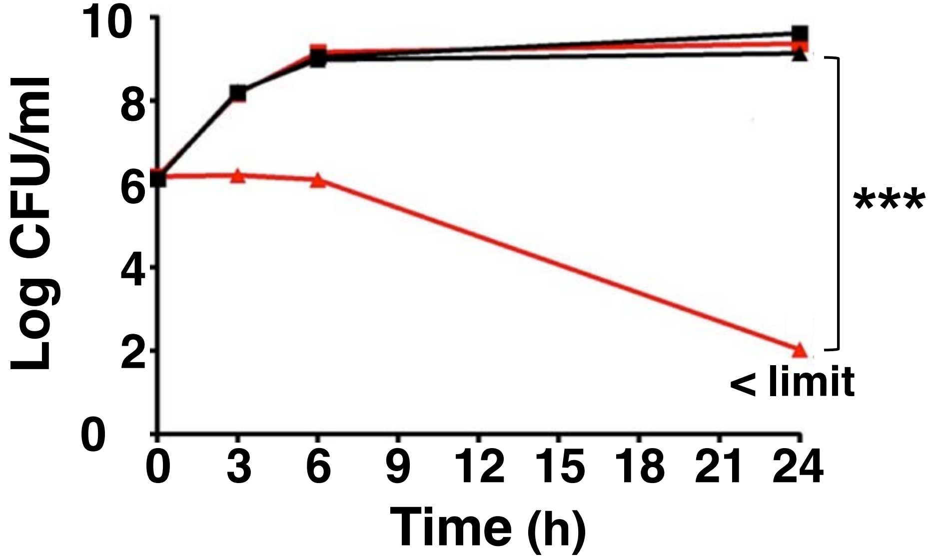
Bacterial Strain	Azithromycin MIC in Ca-MHB (ug/ml)	Azithromycin MIC in 5% LB-RPMI (ug/ml)
MDR Pseudomonas aeruginosa – P4	>64	4
Pseudomonas aeruginosa – PA01	>64	2
Carbapenemase-Producing Klebsiella pneumoniae (KPC) – K1100	32	1
Klebsiella pneumoniae – K700603	64	2
MDR Acinetobacter baumanii – AB5075	32	0.5
Acinetobacter baumanii – AB19606	64	0.25

Leo Lin (UCSD MSTP)

Lin et al. eBiomedicine 2015

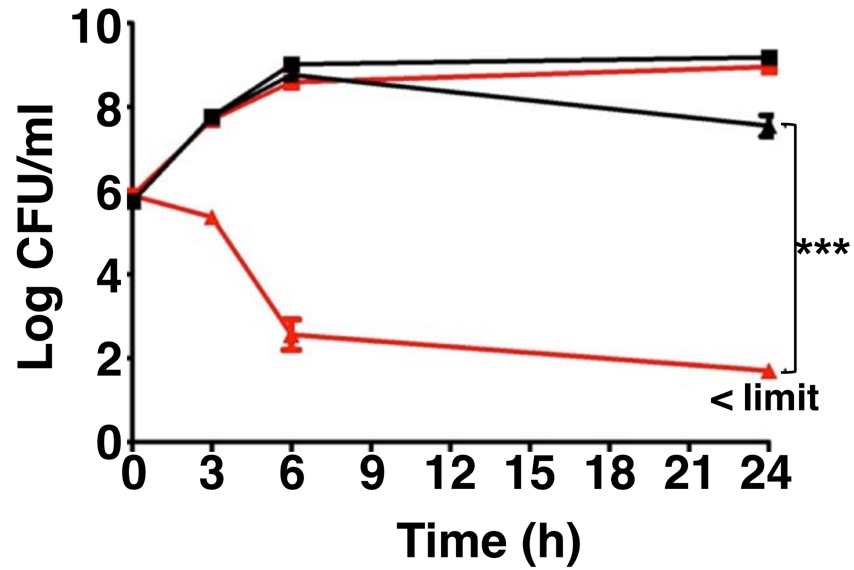
Azithromycin is Cidal for MDR Gram-Negative Rods at low Concentrations in RPMI + 5% LB

MDR *K. pneumoniae*



Ca-MHB ■ No abx
RPMI (5% LB) ▲ AZM 1

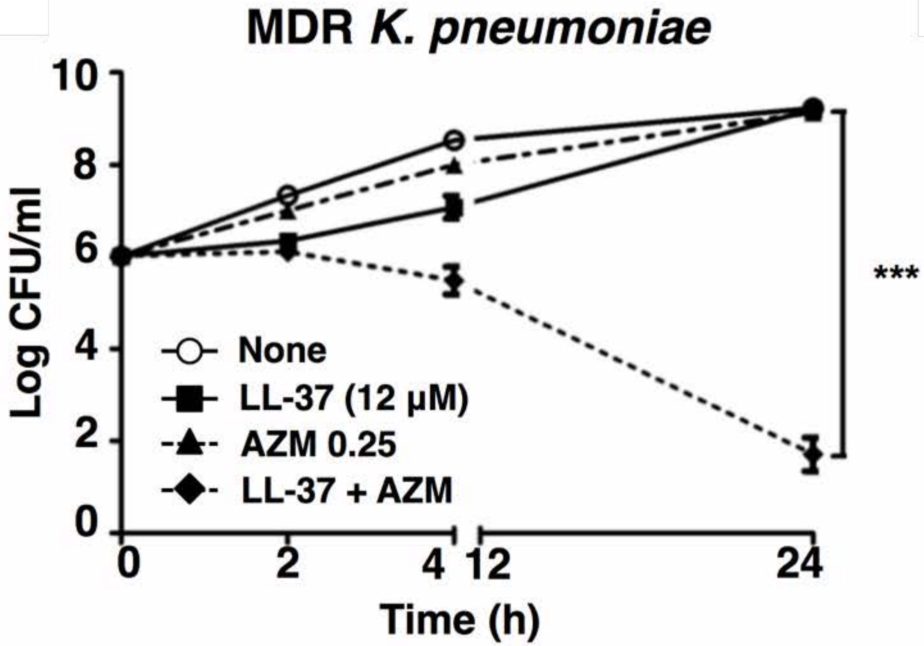
MDR *A. baumannii*

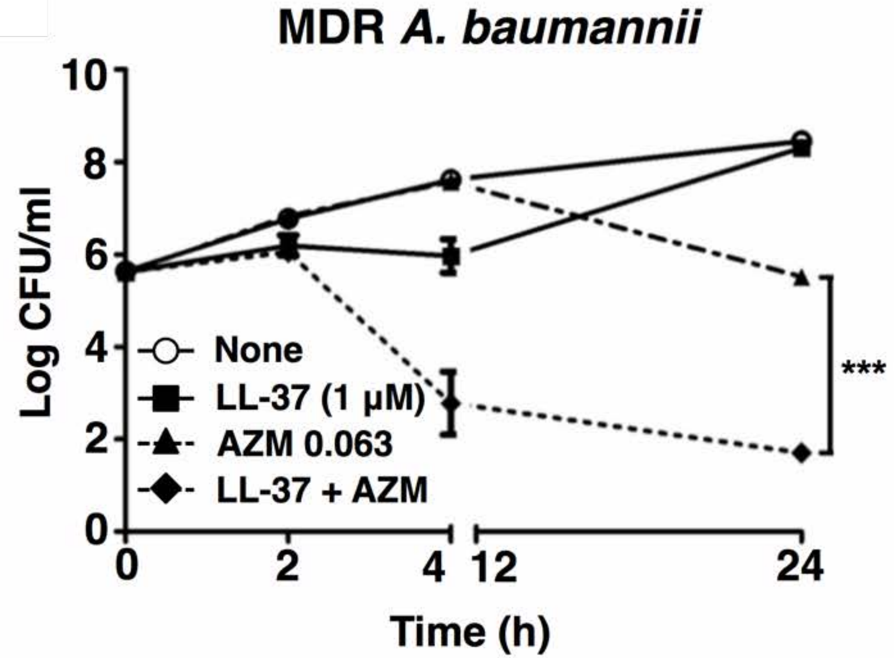


Ca-MHB ■ No abx
RPMI (5%LB) ▲ AZM 0.5

Lin et al. eBiomedicine 2015

Synergy Between Azithromycin and LL-37 in Killing MDR Gram-Negative Rods

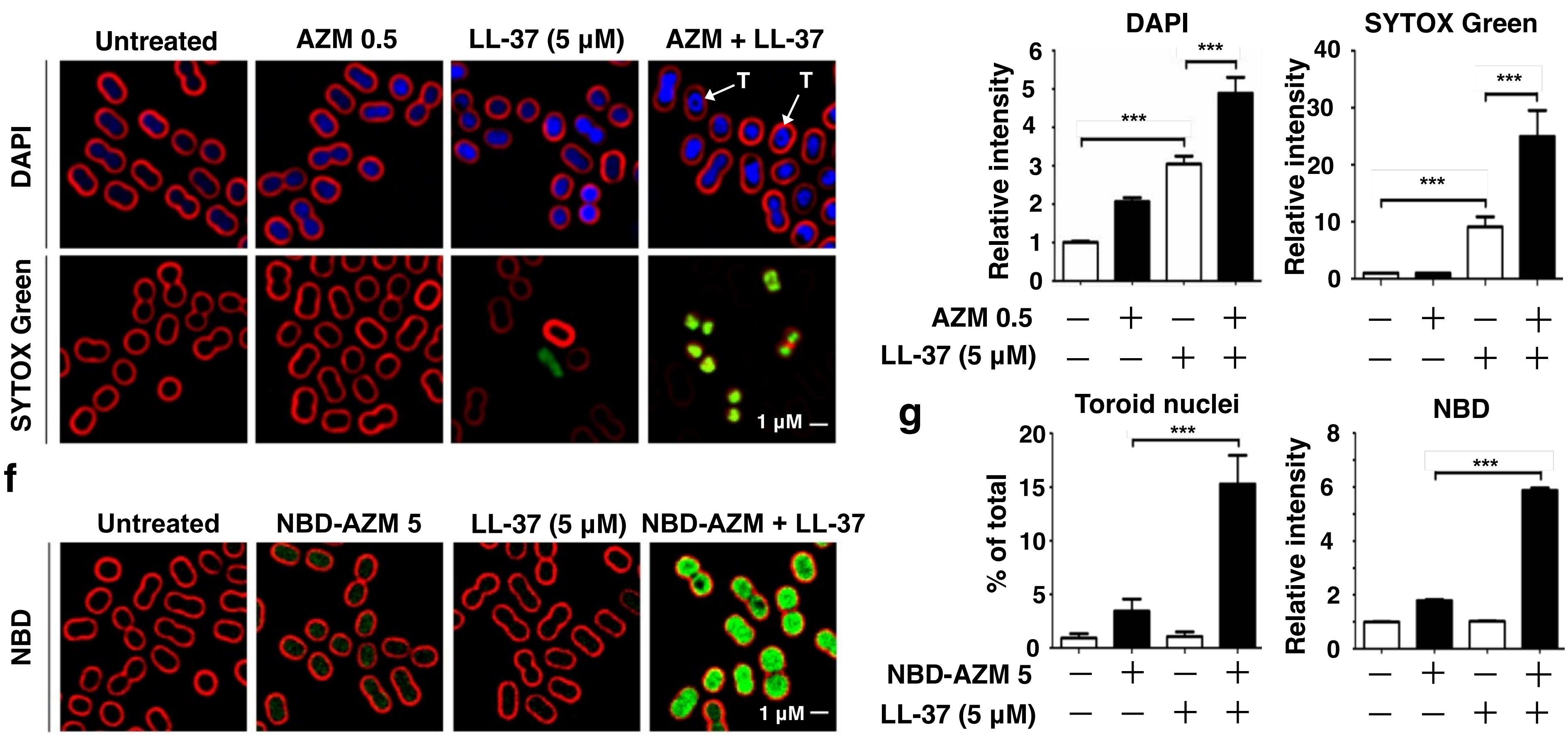




Lin et al. eBiomedicine 2015

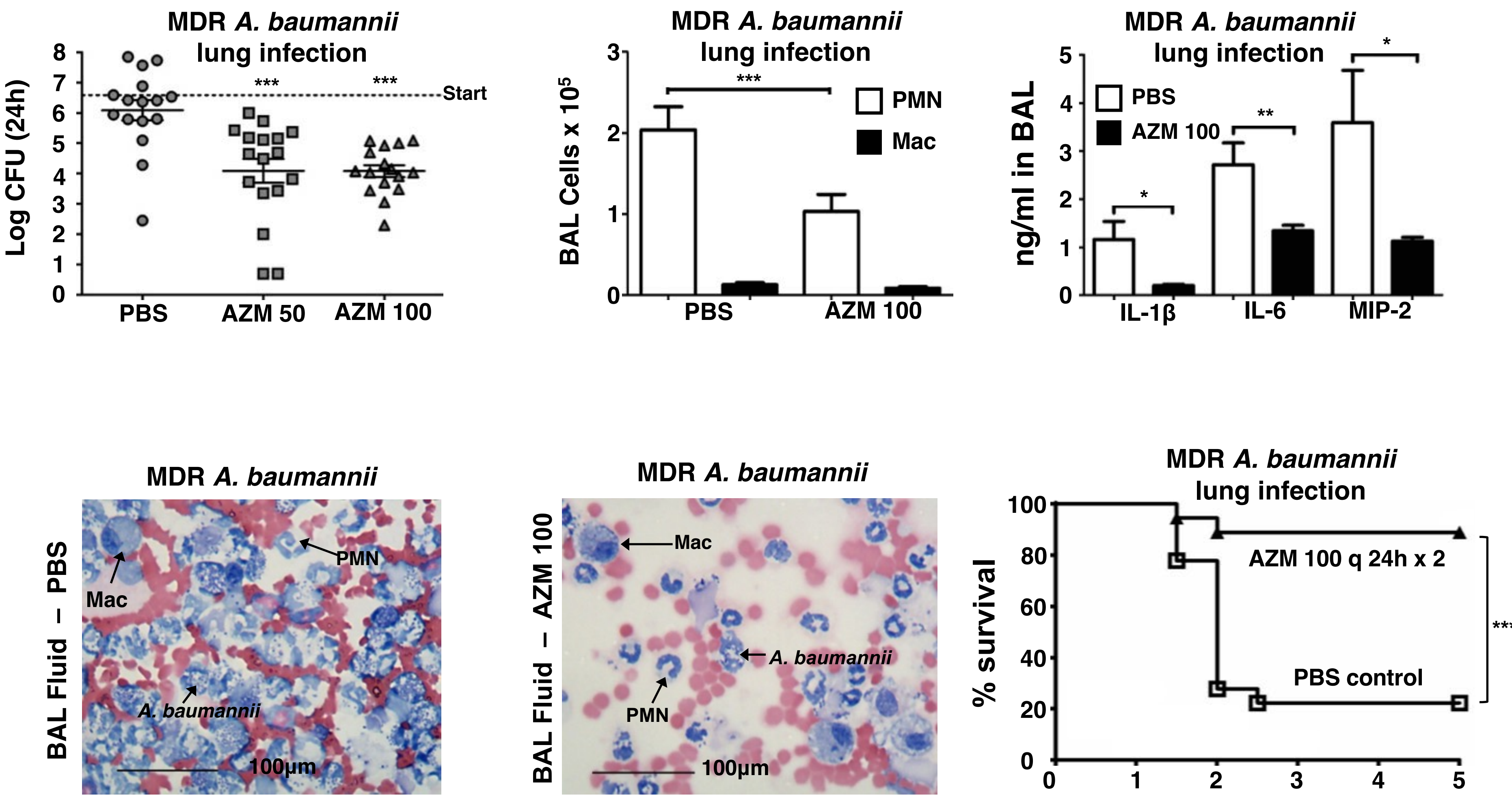
Azithromycin Synergy with LL-37: Increased Cell Wall Permeability and Azithromycin Entry

MDR *Acinetobacter baumannii*

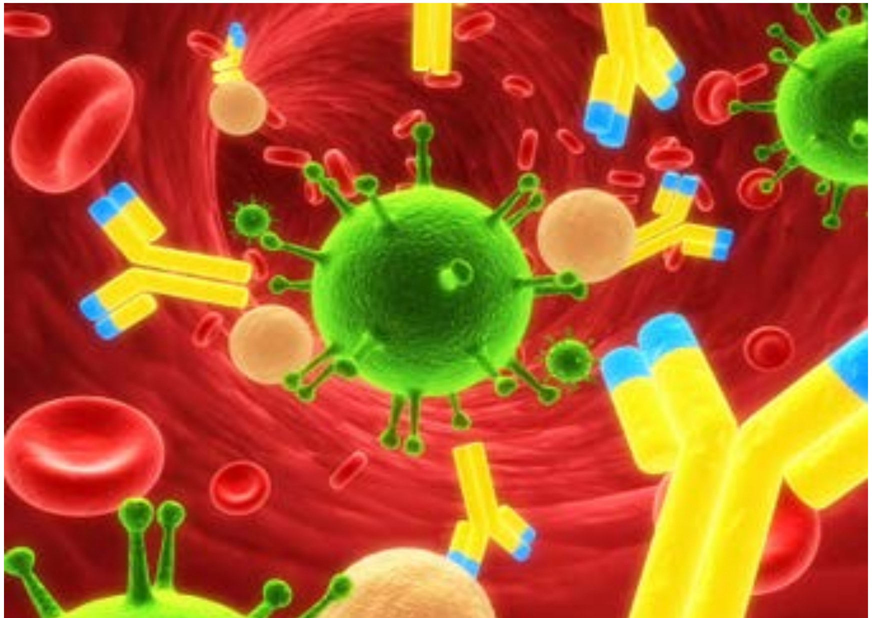


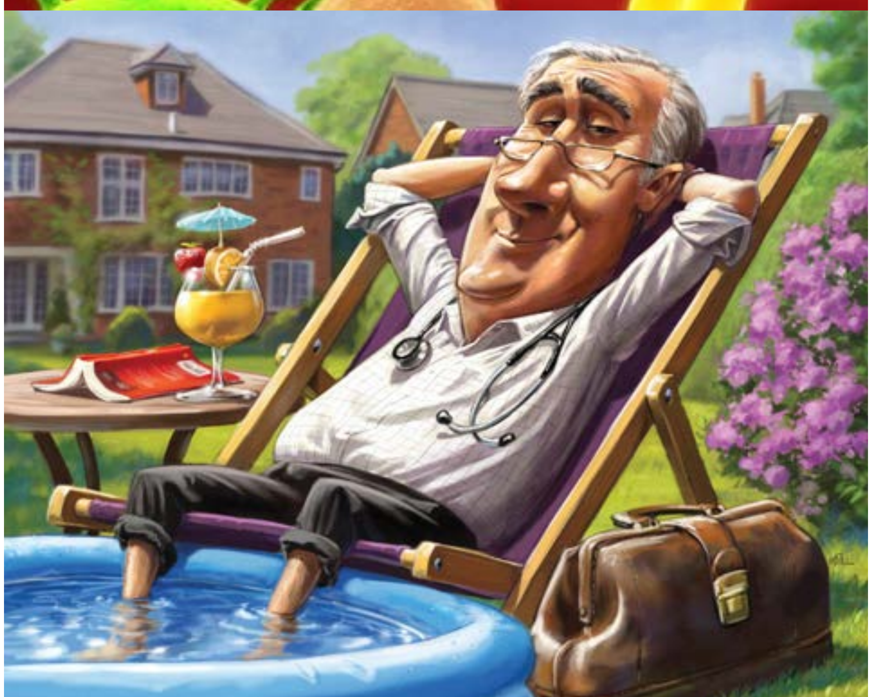
Lin et al. eBiomedicine 2015

Azithromycin Monotherapy Reduces CFU, Lung Inflammation and Mortality in Mouse Model of *A. baumannii* Pneumonia



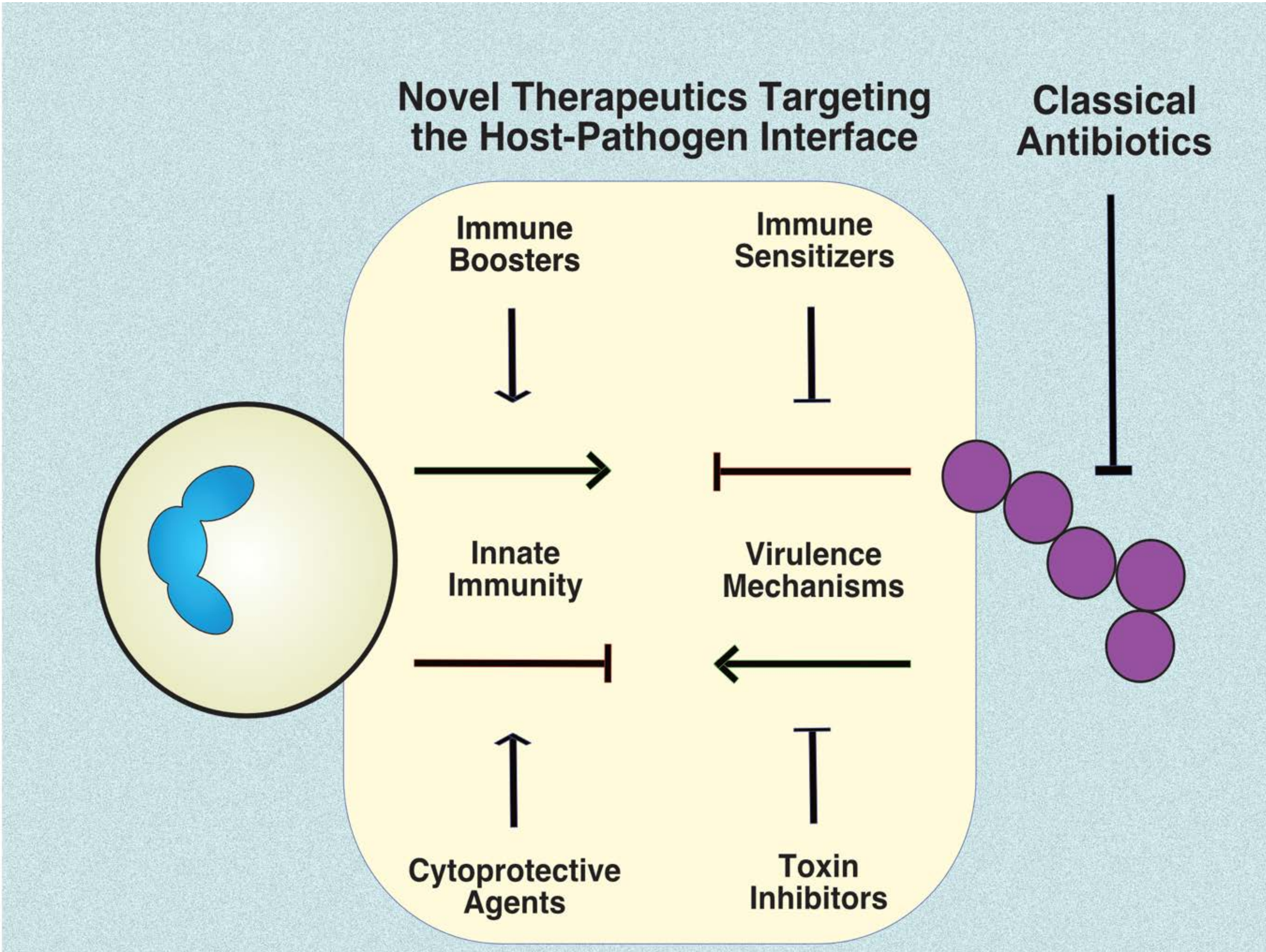
Lin et al. eBiomedicine 2015






TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?


IMMUNOTHERAPY:
Using the Body To Fight Cancer



Munguia & Nizet Trends Pharm Sci 2017

Concept: The Collaborative to Halt Antibiotic-Resistant Microbes

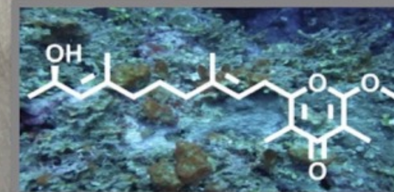
CHARM

@ UC San Diego

Mining novel sources of natural product chemical diversity (the ocean!)

William Fenical
Medicinal Chemistry
Natural Products
Drug Discovery


William Gerwick
Medicinal Chemistry
Natural Products
Drug Discovery

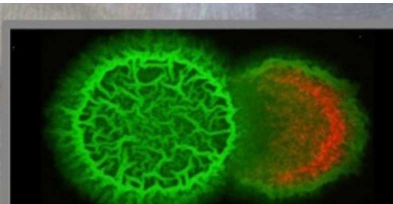



Paul Jensen
Environmental Microbiology
Natural Products
Drug Discovery

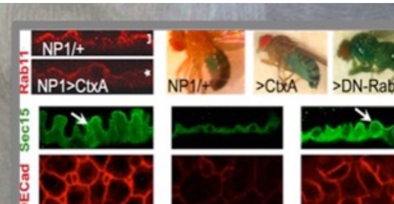

Bradley Moore
Natural Products
Biosynthetic Systems
Drug Discovery


Fundamental microbiology of antibiotic resistance mechanisms, alternative model systems, active genetics

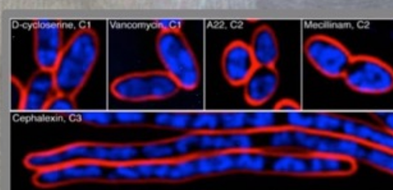
Kit Pogliano
Bacteriology
Microbial Genetics
Drug Discovery

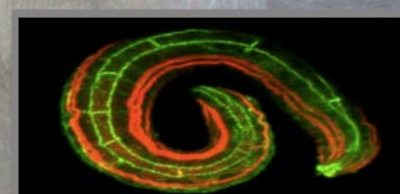
Ethan Bier
Microbial Toxins
Novel Infection Models
Active Genetics

Joseph Pogliano
Bacteriology
Antibiotic Mechanisms
Drug Discovery

Emily Troemel
Host-Pathogen Interaction
Parasitology
Novel Infection Models

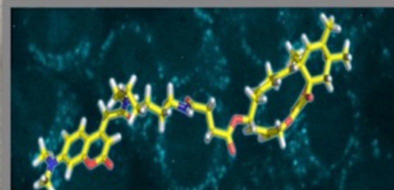



UC San Diego
Chemistry & Biochemistry

Innovative medicinal chemistry approaches to make smarter, safer, targeted antibiotics

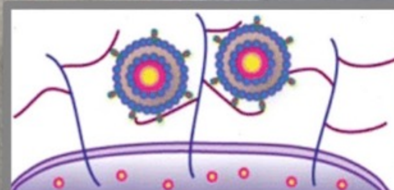
UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences

Michael Burkart
Medicinal Chemistry
Natural Products
Drug Discovery

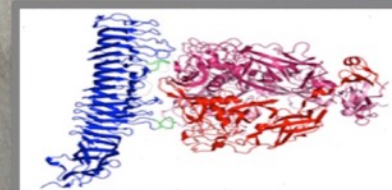


Dionicio Siegel
Medicinal Chemistry
Natural Product Synthesis
Drug Discovery

Yitzhak Tor
Synthetic Chemistry
Antibiotic Mechanisms
Drug Discovery



Partho Ghosh
Structural Biology
Protein Biochemistry
Microbial Pathogenesis

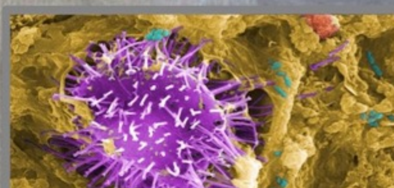


CDIPD
Research
Education
Awareness
Center for Discovery and Innovation in Parasitic Diseases

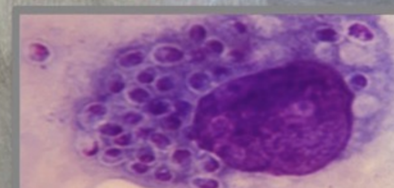
High-throughput screens, chemical genomics, extend to parasitic & emerging viral diseases

CDDI
Center for Drug Discovery Innovation

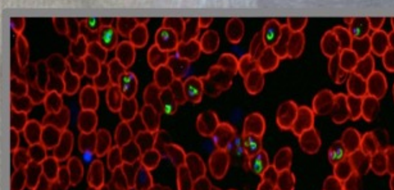
James McKerrow
Neglected Diseases
Parasitology
Drug Discovery



Tariq Rana
Host-Pathogen Interactions
Stem Cell Biology
Drug Discovery



Elizabeth Winzeler
Chemical Genomics
Drug Discovery
Malaria



Lars Eckmann
GI Tract Infections
Mucosal Immunology
Drug Discovery

Center for Microbiome Innovation

Treat infection while preserving the microbiome, modulate microbiome to increase host resistance

iem Institute of Engineering in Medicine

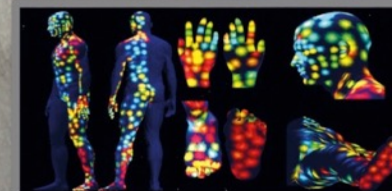
Rob Knight

Human Microbiome
Computational Biology
Microbial Genomics

KNIGHTLAB

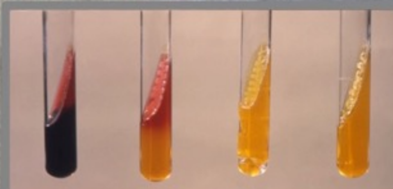
Pieter Dorrestein

Mass Spectrometry
Metabolomics
Human Microbiome



Karsten Zengler

Human Microbiome
Community Systems Biology
Microbial Ecology



David Pride

Human Microbiome
Viral Communities
Antibiotic Resistance

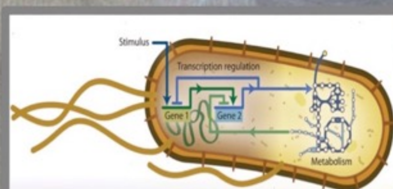
50 YEARS 1966 2016 UC SAN DIEGO BIOENGINEERING Opportunities for Life

Systems biology, big data "–omics" approaches, engineering solutions to diagnosis/treatment

UC San Diego NanoEngineering JACOBS SCHOOL OF ENGINEERING

Bernard Palsson

Systems Biology
Microbial Genetics
Metabolic Dynamics

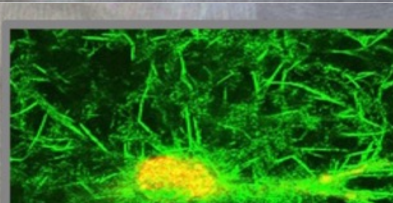


Adam Feist

Systems Biology
Adaptive Evolution
Antimicrobial Resistance

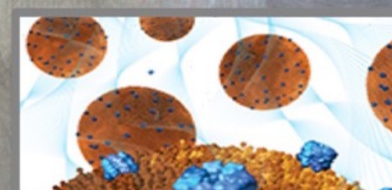
Stephanie Fraley

Bioengineering
Systems Biology
Molecular Diagnostics



Liangfang Zhang

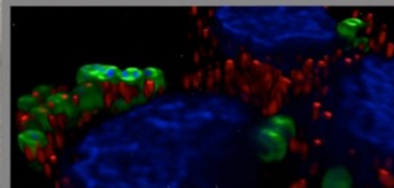
Nanotechnology
Antibiotic Resistance
Experimental Therapeutics



UC San Diego
SCHOOL OF MEDICINE

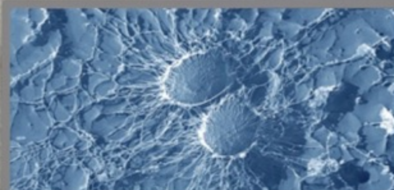
Treat infection as a host-pathogen interaction, block virulence and boost immune clearance

Victor Nizet
Bacterial Pathogenesis
Immunology
Drug Discovery

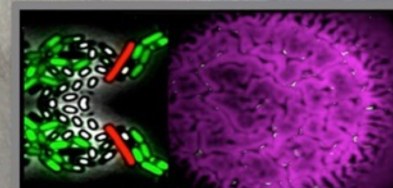


David Gonzalez
Proteomics
Mass Spectrometry
Bacterial Pathogenesis

Richard Gallo
Innate Immunity
Epithelial Biology
Human Microbiome



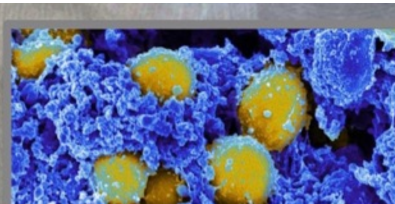
Gürol Süel
Microbial Cell Biology
Single Cell Dynamics
Biofilm Communities



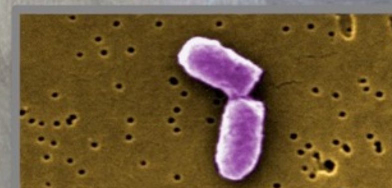
UC San Diego
HEALTH SYSTEM

Analytics of patient data, personalized medicine, novel clinical lab testing, phage therapeutics

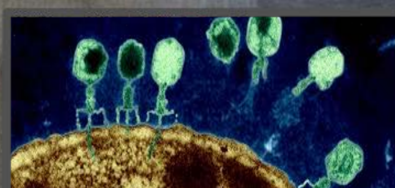
George Sakoulas
Antibiotic Mechanisms
Clinical Pharmacology
Experimental Therapeutics



Sharon Reed
Parasitology
Clinical Microbiology
Drug Discovery



Robert Schooley
Clinical Therapeutics
Antibiotic Mechanisms
Phage Therapy



Monika Kumaraswamy
Antibiotic Stewardship
Clinical Therapeputics
Infection Control

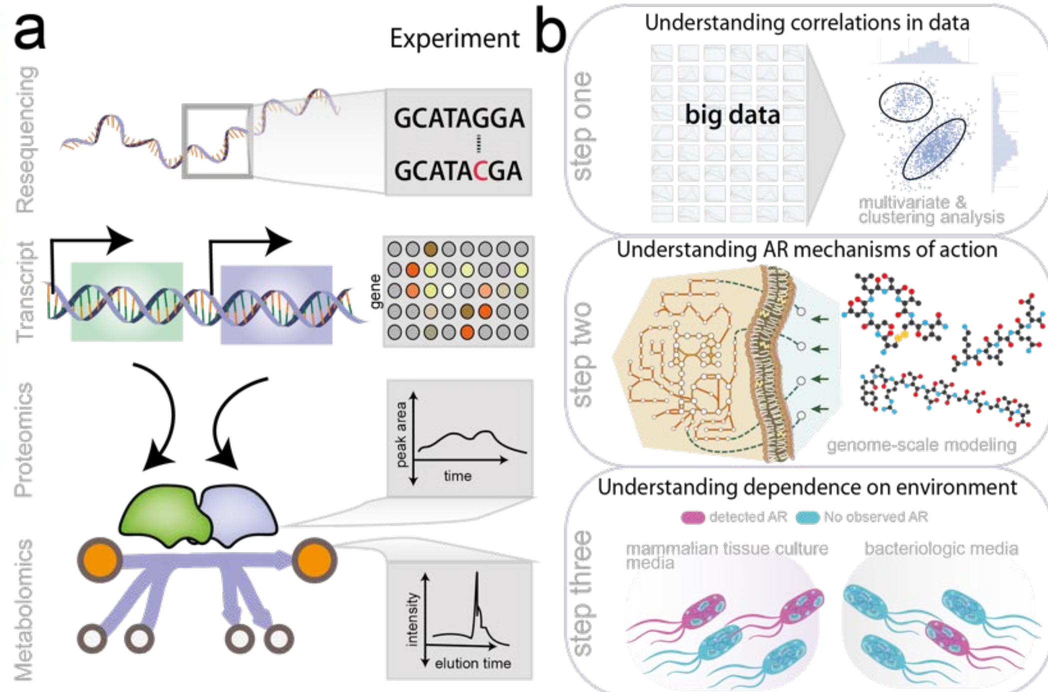
New NIH/NIAID U01 (Palsson/Nizet/Pogliano/Sakoulas/Dorrestein/Knight/Feist)

"Systems Biology Approach to Redefine Susceptibility Testing and Treatment of MDR Pathogens in the Context of Host Immunity"

Scientists Receive $9.5M NIH Grant to Combat Antibiotic Resistance

Researchers at University of California, San Diego School of Medicine have received a five-year, $9.5-million award from the National Institute of Allergy and…

DDDMAG.COM

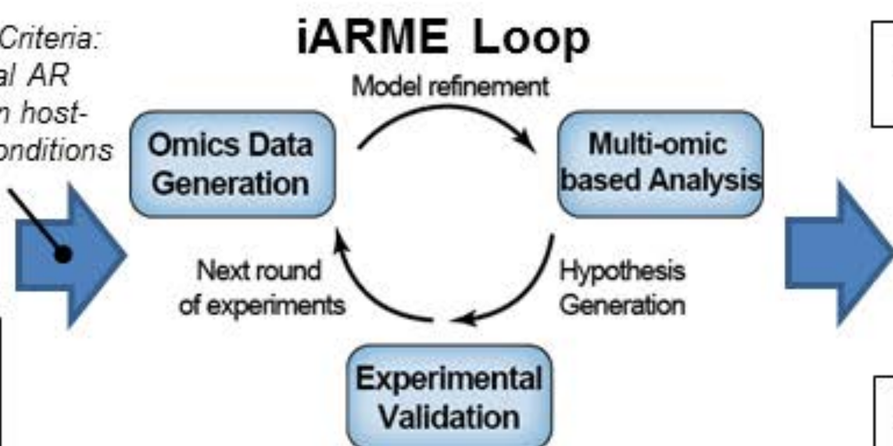


Antibiotic Resistant Strains:

- *K. pneumoniae*
- *A. baumannii*
- *P. aeruginosa*
- *S. aureus*

4 new antibiotic / target pathogen / host-factor combinations per year

Loop Entry Criteria: Differential AR response in host-mimicking conditions



Treatment Options with Current Antibiotics

Host-Pathogen and Pathogen-Drug Interaction Mechanisms

Resistance Mutations and Comparison to Clinical Isolates

Multi-omics Database and Genome-scale Models


$1.50 PLUS TAX

The San Diego Union-Tribune

UTSanDiego.com

THURSDAY • JUNE

OBAMA ORDERS BOOST IN U.S. TROOPS TO IRAQ

450 will be deployed as White House struggles to reverse gains by Islamic State

ASSOCIATED PRESS & THE WASHINGTON POST

WASHINGTON

President Barack Obama ordered the deployment of up to 450 more American troops to Iraq on Wednesday in an effort to reverse major battlefield losses to the Islamic State, an escalation but not a significant shift in the struggling U.S. strategy to defeat the extremist group.

The U.S. forces will open a fifth training site in the country, this one dedicated specifically to helping the Iraqi army integrate Sunni tribes into the fight, an element seen as crucial to driving the Islamic State out of

SEE IRAQ • A6

Cpl. Keegan Merlino, an infantryman with the 82nd Airborne Division, instructs Iraqi army soldiers during a breach assault and building clearance course at Besmaya Range Complex, Iraq. U.S. ARMY PHOTO

STUDY: COMMON ANTIBIOTIC WORKS ON SUPERBUGS

UCSD researchers find azithromycin kills drug-resistant bacteria in body

BRADLEY J. FIKES • U-T

In the fight against deadly drug-resistant infections, UC San Diego researchers have discovered a potential new weapon from an unexpected source. It's a common antibiotic that doctors long ago dismissed as ineffective against superbugs.

The antibiotic is azithromycin, sold under the name Zithromax Z-Pak. It's the most commonly used antibiotic in the United States and is prescribed for pneumonia, and skin and throat infections.

SEE ANTIBIOTIC • A9


MULTIPLE CHOICES

The San Diego Union-Tribune

SD IN DEPTH SUNDAY

SAN DIEGO NEWSMAKERS, IDEAS + OPINIONS

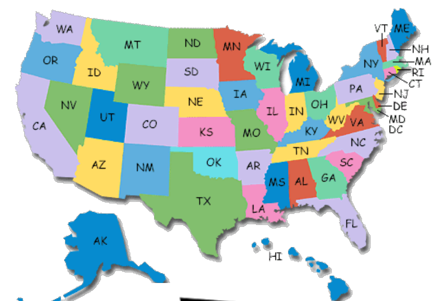
TARGETING SUPERBUGS

Antibiotics, a breakthrough of modern medicine, have fallen behind increasingly resistant forms of bacteria. Now, scientists and public health advocates are redoubling efforts to defend against aggressive infectious diseases.


RESEARCH

"Ideally, we want to have a pill that kills the bad guys and doesn't touch the good guys."

"Antibiotic resistance, at its core, is really the best example we have of Darwinian natural selection."



CHARM

OVERARCHING GOAL

Establish UC San Diego and its La Jolla Mesa Partners as a global leader in innovative, paradigm-shifting, research-driven solutions to combat the Antibiotic Resistance Crisis, which will inevitably become a public health and national security emergency for the coming generation.

CHARM

NEXT STEPS

Selected to move forward - new Health Sciences Strategic, with
potential for Institute of Engineering in Medicine to partner

Fundraising strategy to be developed – meetings this week w/

Ruben Flores (Office of Innovation & Commercialization)

Working with CARB-X (NIH/DOD/Wellcome Trust) Accelerator – 3
projects already funded with UCSD investigators

International Partners lined up (CCCID-China, Amrita U-India,
Utrecht, Queensland, Pasteur, Karolinska)

Launch website and social media presence by Winter Quarter ’18

FORMER LAB

Yung-Chi Chang (National Taiwan U.)
Ismael Secundino (UNAM-Cuernava)
Nina van Sorge (Utrecht Univ.)
Suzan Rooijakkers (Utrecht Univ.)
Maren von Köckritz-Blickwede (U. Hanover)
Cheryl Okumura (Occidental)
George Liu (Cedars-Sinai)
Kelly Doran (San Diego State)
Carole Peyssonnaux (Instiute Cochin)
Annelies Zinkernagel (U. Zurich)
Laura Crotty Alexander (UCSD)
Amanda Lewis (Wash. U. St. Louis)
Shauna McGillivray (Texas Christian U.)
David Gonzalez (UC San Diego)

http://nizetlab.ucsd.edu

COLLABORATORS

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