Starting an antibacterial drug discovery screening programme

Guest speakers: Bruce Blough & Gerry Wright

Moderator: Philip Gribbon

Host: Shirine Derakhshani (GARDP)

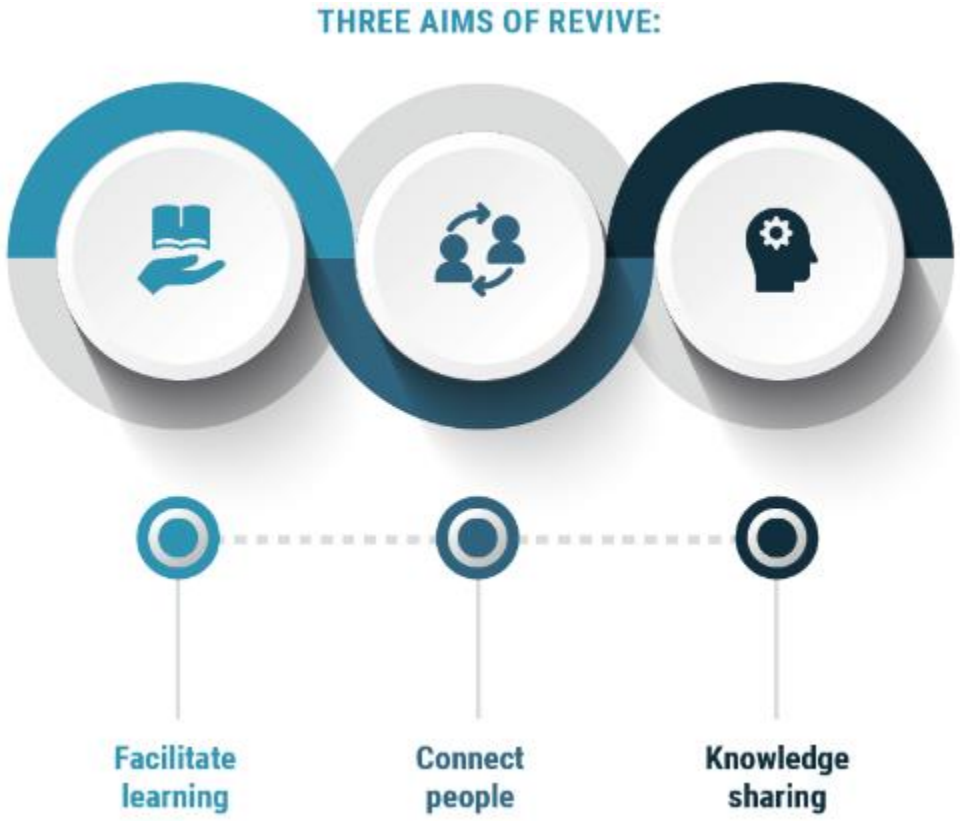
5 September 2023

GARDP

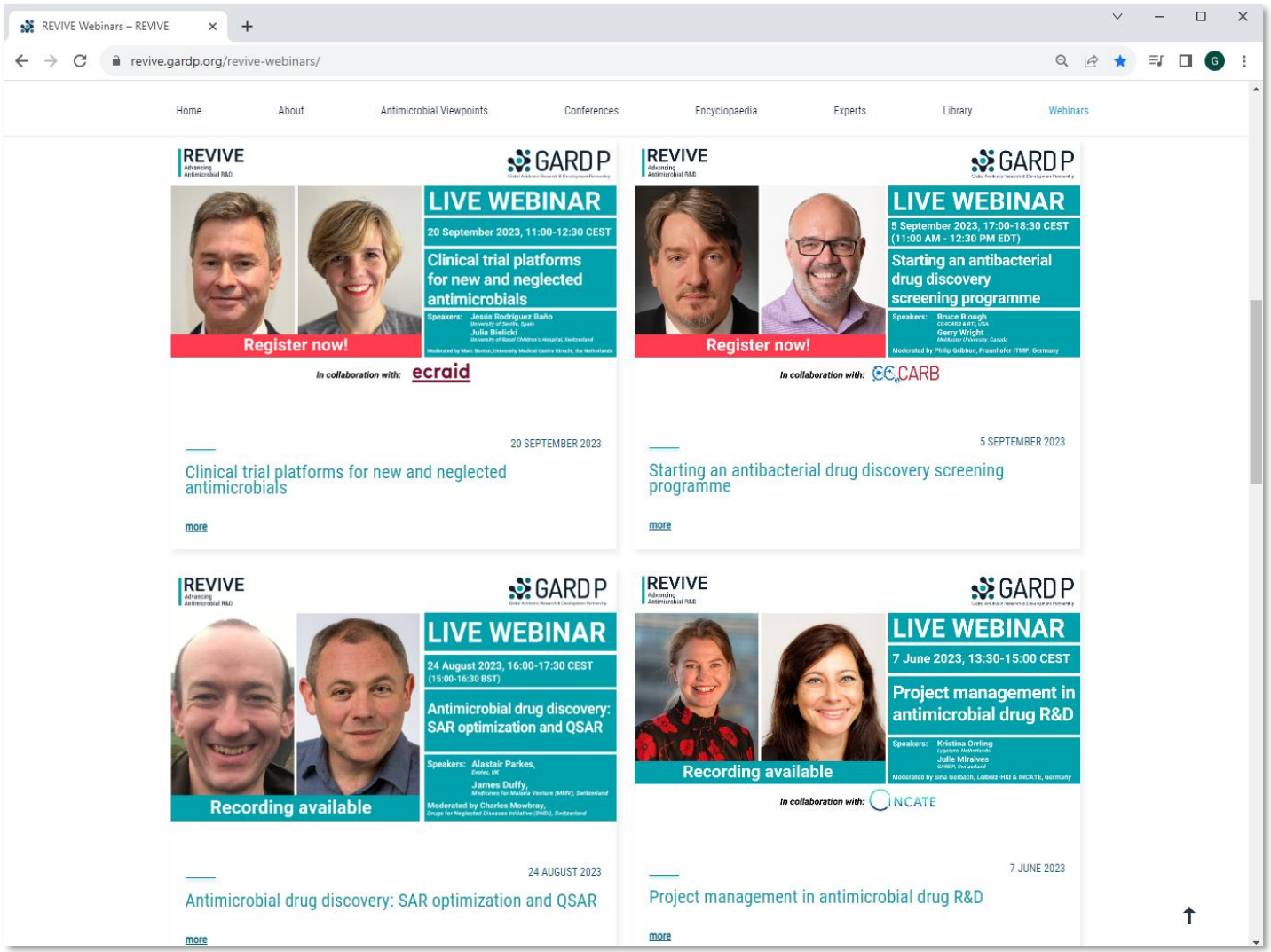
Global Antibiotic Research & Development Partnership

REVIVE

Capture essential R&D technical knowledge and share expertise with the global community through the REVIVE website (revive.gardp.org).



Webinar recordings



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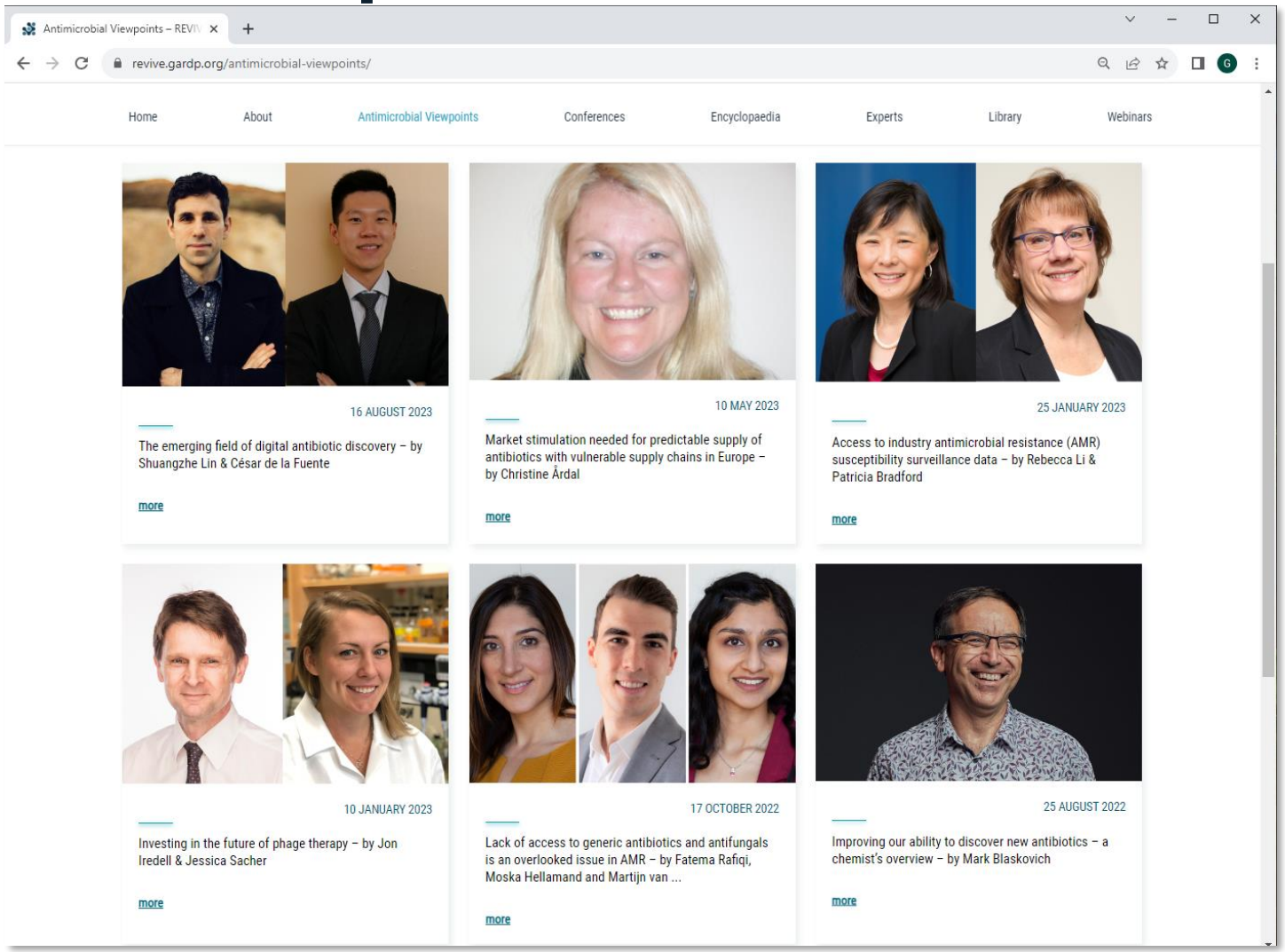
Antimicrobial Viewpoints



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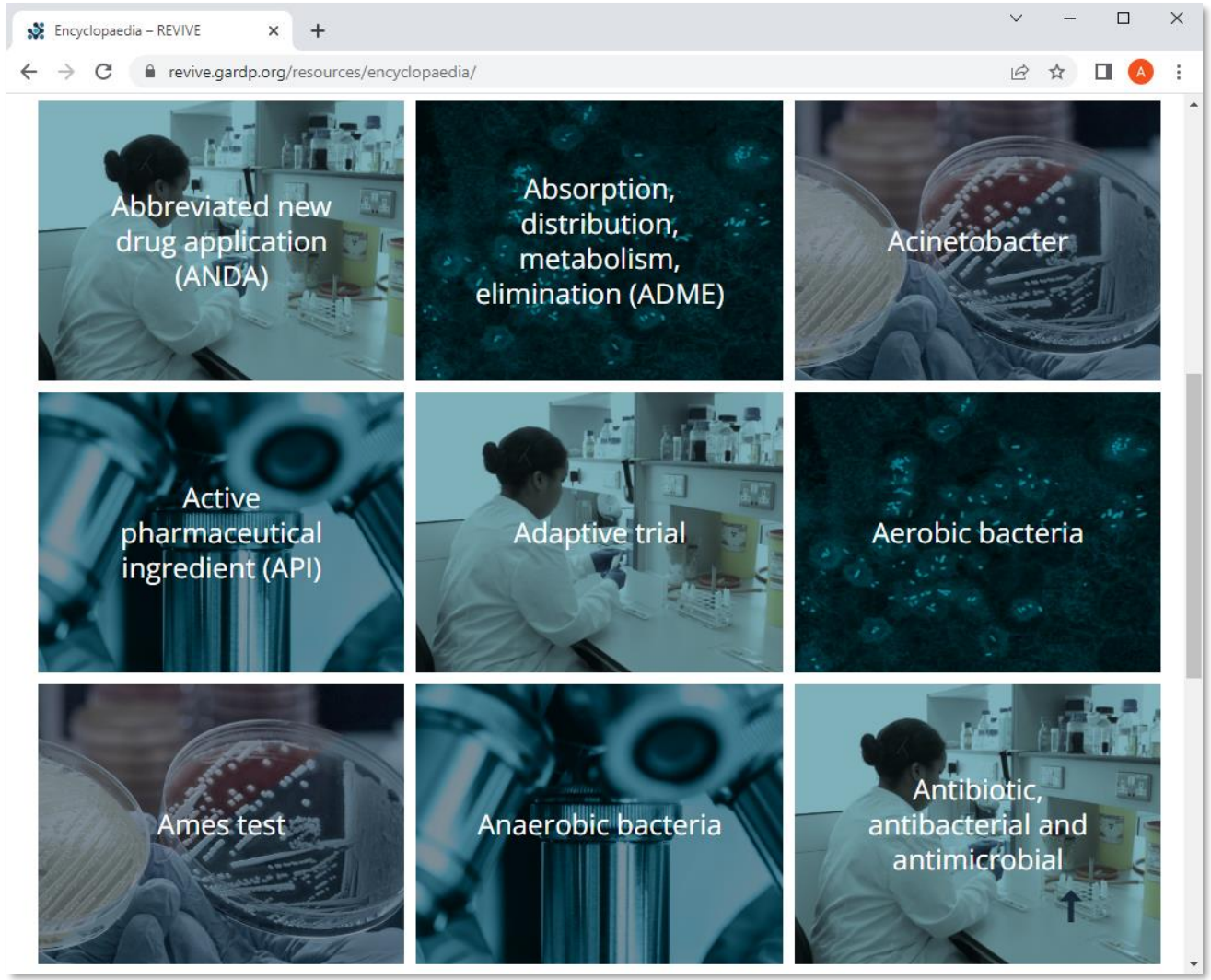
Antimicrobial Encyclopaedia



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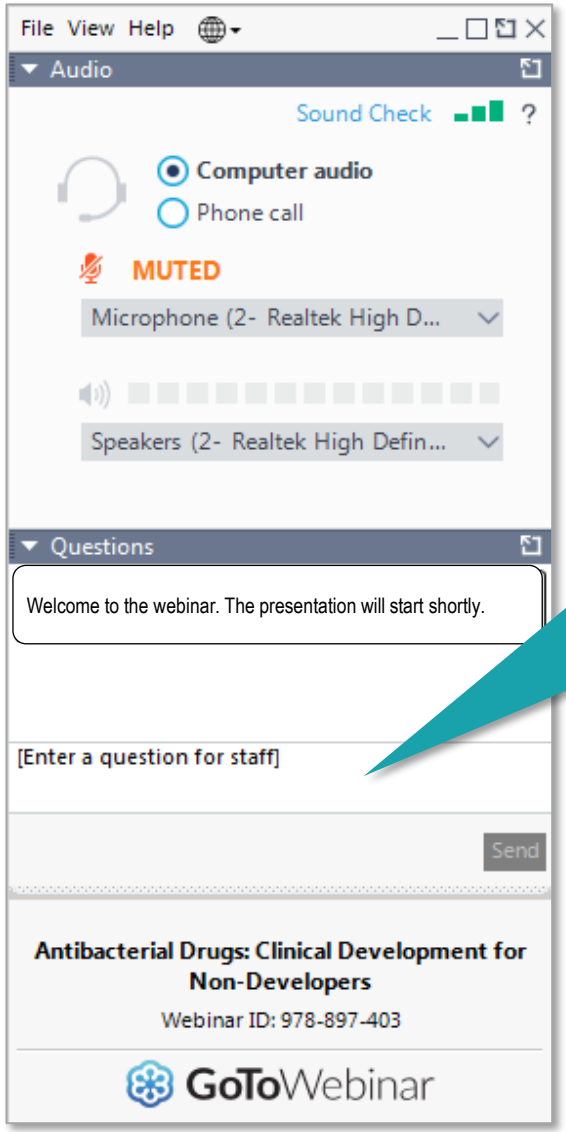
How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

This webinar was developed in collaboration with CC4CARB.

CC4CARB

Chemistry Center for Combating Antibiotic Resistant Bacteria

https://www.cc4carb-collection.org/

Today’s speakers

Starting an antibacterial drug discovery screening programme

Bruce Blough
Principal Investigator and Senior Research Chemist
Chemistry Center for Combating Antibiotic Resistant Bacteria – CC4CARB
& RTI International (USA)

Gerry Wright
Professor
DeGroote Institute for Infectious Disease Research, McMaster University (Canada)

Moderator:
Philip Gribbon
Head of Discovery Research
Fraunhofer Institute for Translational Medicine and Pharmacology – ITMP (Germany)

Bruce Blough

Bruce Blough is a Senior Research Chemist in the Center for Drug Discovery (CDD) at RTI International and the Principal Investigator for CC4CARB. He has more than 30 years of experience in drug discovery as a medicinal chemist, leading many projects including therapeutics targeting drug abuse (cocaine, nicotine, methamphetamine, opiates), weight loss, depression, Alzheimer's disease, and infectious diseases.

In addition, he has been on several teams that led to clinical trials, including RTI-336 for cocaine addiction, and the progesterone receptor modulator ulipristal acetate (Ella, EllaOne, Esyma) for uterine fibroids. He is particularly interested in natural products and microbial signaling. He has experience in all phases of the drug discovery and development process and has been a key leader within CDD.

Bruce is a graduate of Wake Forest University (USA) with a B.S. degree in chemistry, and the University of South Carolina with a Ph.D. degree in Organic Chemistry.

Building a Gram-Negative Focused Screening Library

Bruce Blough, Ph.D.
Center for Drug Discovery
RTI International

September 5, 2023

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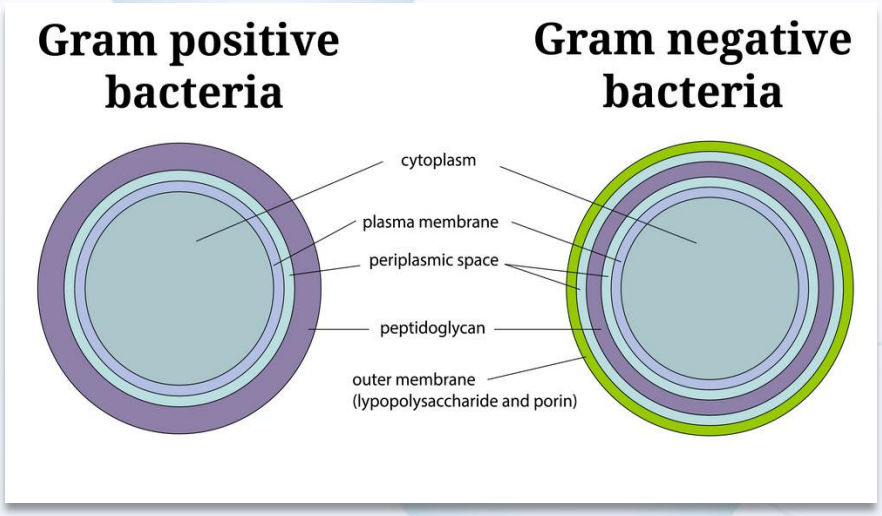
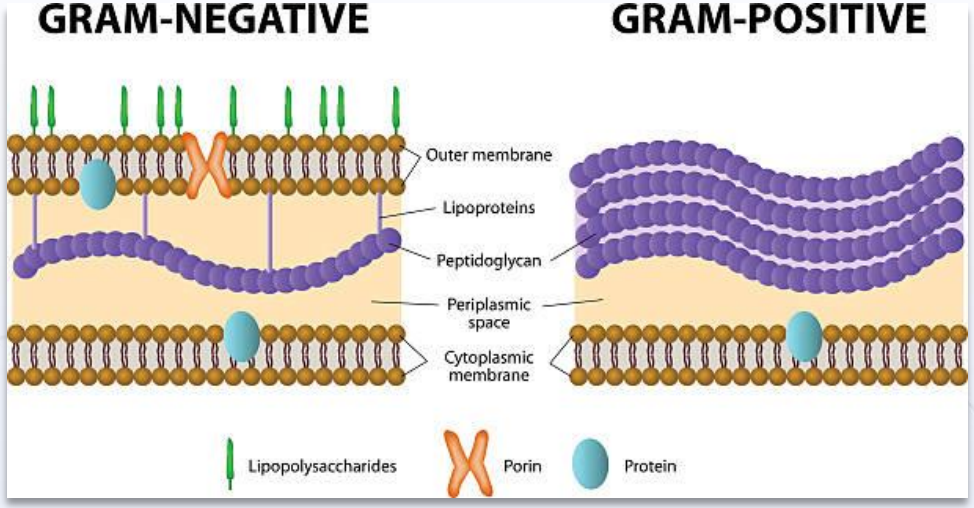
Chemistry Center for Combating Antibiotic Resistant Bacteria (CC4CARB)

- An **innovative and unique chemistry center** targeting Gram-negative antibiotic drug discovery
- **Goal:** Synthesize a library of **Gram-negative related chemical matter** and distribute to the public for screening and/or testing
- **Purpose:** There is a **lack** of clinically available **Gram-negative antibiotics** and a **lean clinical pipeline** for development
- **Funding**: NIH/NIAID
- **RTI Vision**: a **front-end drug discovery** piece of the Public Private Partnership landscape (i.e. CARB-X)

Biological Problem: Cell Walls





- **Gram-positives: 2 layers**, the outer layer being a stainable peptidoglycan layer
- **Gram-negatives: 3 layers** making them harder to penetrate and enabling a higher level of defense (e.g. efflux pumps)

Discovery Problems: Screening Failures/Barriers to Novelty

- Big pharma screening libraries ***failed***
  - Million compound libraries failed to find novel scaffolds
  - Pharma libraries = **mammalian cell focused**
  - Types of compounds found to penetrate Gram-negatives are not in typical pharmaceutical libraries often considered liabilities (1° amines, “eNTRy” rules)
- Systemic barriers for **novel** scaffolds
  - Need MOA and safety data to avoid “bleach” and toxins
  - Very little early funding to move novel scaffolds ***to sustained fundability*** (venture capital, grants, etc.)

CARB
Chemistry Center for Combating Antibiotic Resistant Bacteria

Solution: CC4CARB

***Build** a Gram-negative focused **screening library** by **targeting novel scaffolds** from individual researchers.*

- Synthesize novel focused scaffold libraries (40-200 compounds) to seed/facilitate discovery efforts
- Enable sustained fundability for individual researchers
  - Biotech: ***Generate IP asset*** for Venture Capital funding
  - Academics: ***Generate prelim data*** for grants
- Combined, will have built a collection of compounds (~6,000) focused on structural features and scaffolds favorable to Gram-negative antibiotic discovery/penetration
- Provide a diverse screening library to address new/other microbes and related issues

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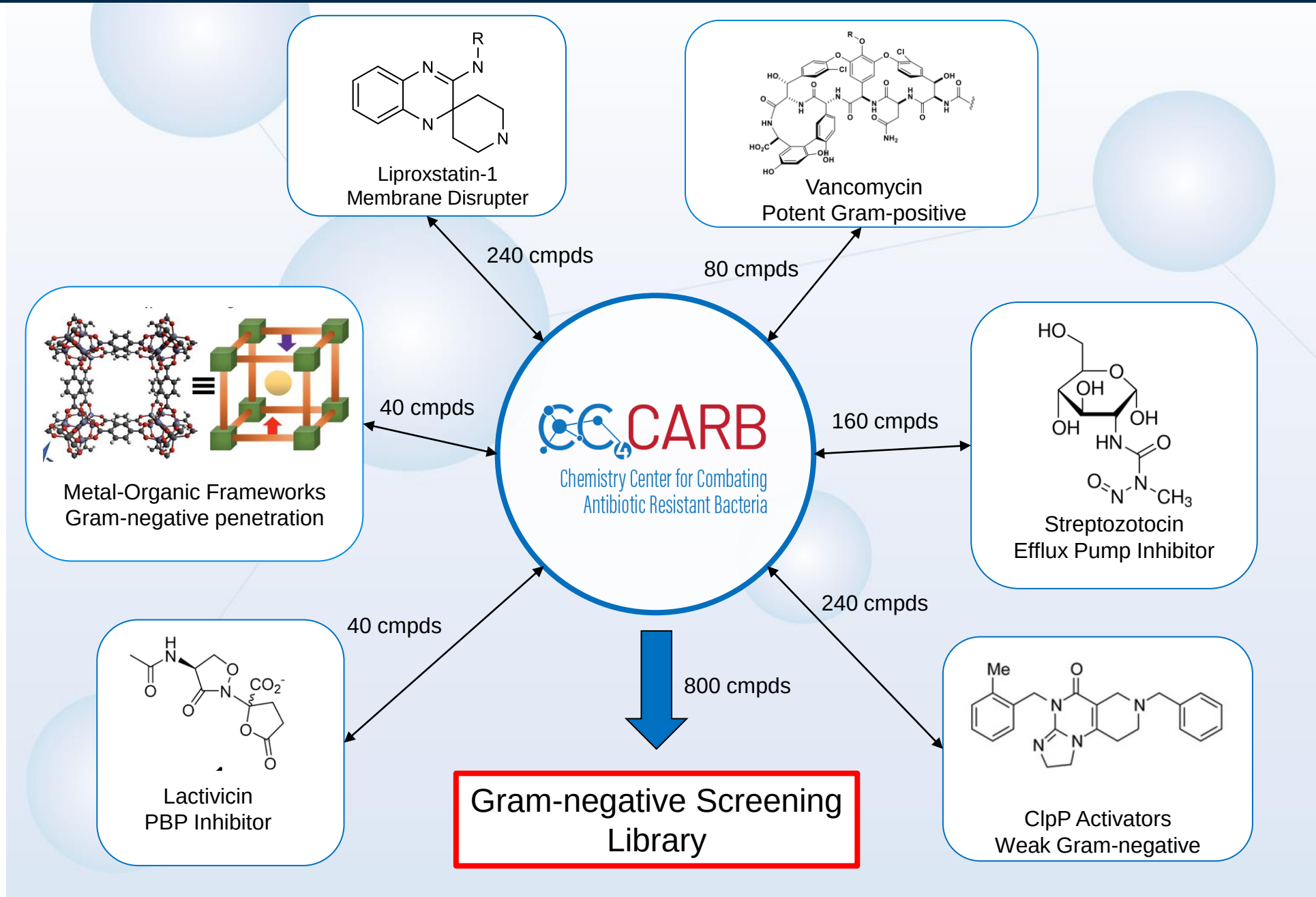
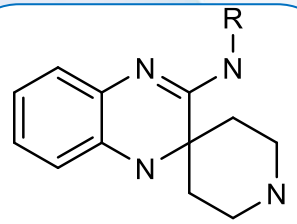
Build screening library from individual projects



CC4CARB Process Overview

AMR Community

Solicit



Liproxstatin-1
Membrane Disrupter

Scaffold Idea

Synthesize

15 FTEs
>25 mg/cmpd
>95% pure

Donations
Acquisitions

Scaffold Library

Distribute

Adjunct Testing

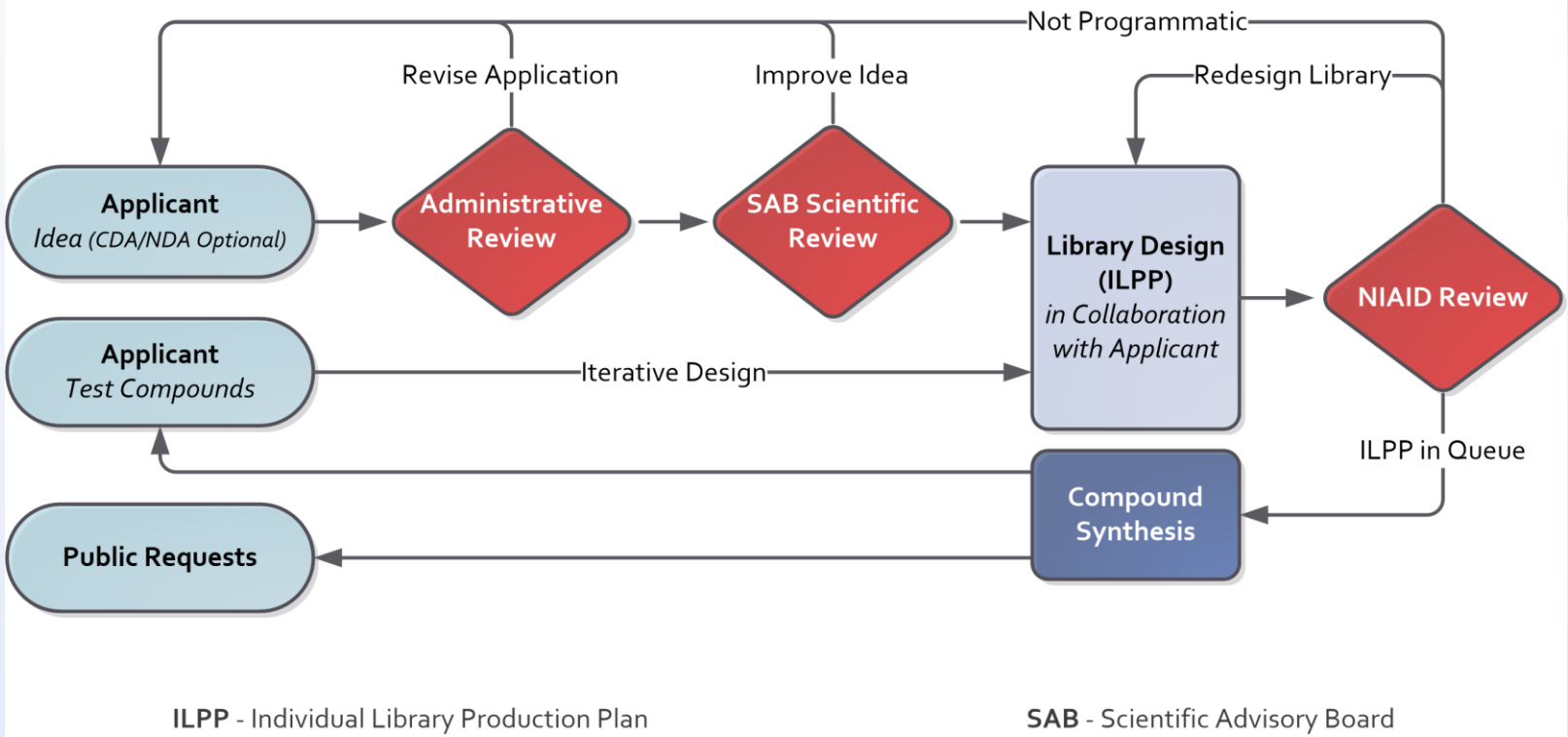
MIC data

Contributor
(5 mg/cmpd)

Community
(screening plates)

CC4CARB
Chemistry Center for Combating Antibiotic Resistant Bacteria

Specific CC4CARB Proposal Process



ILPP - Individual Library Production Plan

SAB - Scientific Advisory Board

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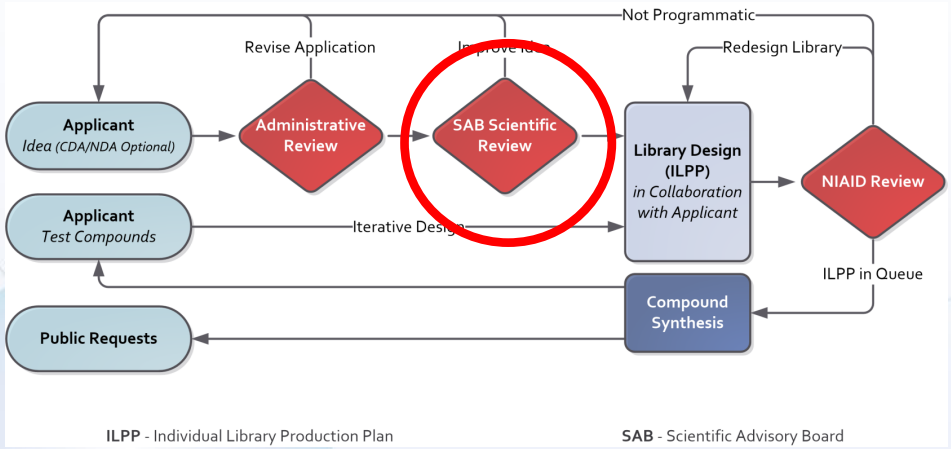
NIH Style Proposal Review: SAB



Current Scientific Advisory Board Members:

- **Paul Hergenrother,** Ph.D. (U. of Illinois): Numerous awards for research and innovation in anti-infectives and cancer. Devised “eNTRy” rules for Gram-negative penetration
- **Michael Barbachyn**, Ph.D. (Calvin College): Leading antibiotic inventor at several large pharmaceutical companies including Upjohn, Bristol-Myers, Pfizer, and Astrazeneca. Co-invented oxazolidinone class of antibiotics (5 in clinic or in trials)
- **Alice Erwin**, Ph.D. (Consultant): Studied Gram-negative resistance and contribution of membranes. Led antimicrobial programs at PathoGenesis, Chiron, and Vertex
- **Andrew Calabrese**, Ph.D. (Revagenix): Co-founder of several biotechs including Revagenix. Co-invented Cligcosiban™ and SpinoMetis™
- **Brian Conlon**, Ph.D. (U. of North Carolina): Studies antibiotic efficacy in complex host environment targeting treatments to eradicate chronic infections (persisters)

IP Embargo Period

- **18-month** non-disclosure
  - 1 year library synthesis + 6 months testing/assessment
  - Clock begins with formal **synthesis plan approval**
- Can be **extended** with NIAID approval

- Legal Issues:
  - IP **inventorship** dependent on design involvement per patent law
  - IP **ownership** is between the contributor and RTI and will be given to the contributor unless there is an ongoing or future relationship

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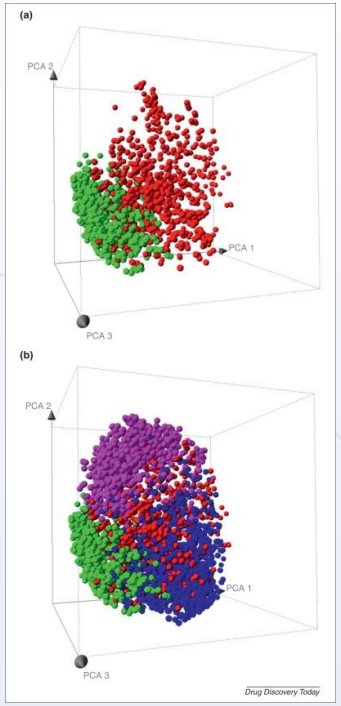
CC4CARB 5 Year Goals and Current Progress

5 Year Goals	30-Month Progress
6-12 Months to build process	Synthesis (NIAID): **2 Months** Website: **4 Months** SAB KO: **7 Months** First external project reviewed: **13 Months** First external project synthesis: **16 Months**
~50 Projects	SAB has reviewed **35 Proposals** (7 NIAID) • 5 rejected • 1 in process of review NIAID has approved **27 scaffolds/ILPPs** • 3 Donation/purchases • 5 additional accepted and in design phase
>6,000 Compound Library	**~2050** Compounds to date **~1240** Compounds tested for activity
25 publications/patents	**3 Publications** written but not submitted **1 Patent** filed **2 Spin-off Proposals**

Library Diversity

- **Can't make 6,000** totally unique and diverse compounds
  - Cost prohibitive
  - Unique methodology development, materials, labor
- **Make sets**: 10 Analogs of 20 scaffolds >> 200 of 1 scaffold
- Medicinal chemistry goals vs library goals: ***Balance!***
  - Contributor project goals: **Less diverse, low efficiency**
  - NIAID library goals: **More diverse, high efficiency**
- **Incorporate** as much **diversity** within a library as possible at beginning
- Accept scaffolds not represented in the commercial space/literature
- Adding functionality not well represented in existing libraries: 1° amines



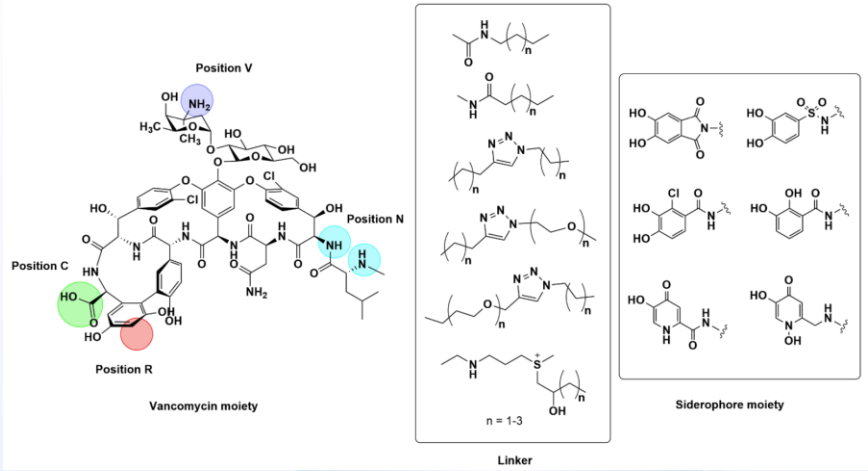
Chemistry Center for Combating Antibiotic Resistant Bacteria

Gram-negative Design

- **Solicit unique scaffolds** with Gram-negative activity
- **Rescue known** Gram-negative scaffolds
  - Overcome resistance
- **Hergenrother** "eNTRy" Rules: *Richter, M., et al. Nature 545, 299–304 (2017).*
  - Ionizable Nitrogen: 1° amine/guanidine
  - Low globularity: flat is better (0.25)
  - Low flexibility: reduce rotatable bonds
- **Siderophores**
  - Hijack iron accumulation/sequestration processes like TonB
- **AI** and **Machine Learning**
  - Modeling medicinal chemist intuition: "*Looks like a bug drug*"
- **Another potential moiety** avoided in mammalian drug design

CARB
Chemistry Center for Combating Antibiotic Resistant Bacteria

Design Example: Vancomycin Siderophores



Compound	MIC (mg/L) [a, b, c] EC	EC efflux-	KPN	PSA	PSA efflux-	ACB	SA	GC
Erythromycin	>8	2	>8	>8	>8*	4	0.25	1
Levofloxacin	0.016	0.004	0.5	0.125	0.008	0.016	0.125	>2
Tetracycline	1	0.5	>8	>8*	0.5	1	0.125	4
vancomycin	>64*	>64	>64	>64*	>64*	64	1	32
V8	32	64	>64	>64*	>64*	2	16	>64
V10	16	>64*	>64	>64*	>64*	2	4	>64
V11	8	>64*	>64	>64*	>64*	1	2	>64
V12	8	>64*	>64	>64*	>64*	1	4	>64
V14	64	64	>64	>64*	>64*	1	4	>64
V15	64	64	>64	>64*	>64*	2	4	>64
V17	16	>64	>64	>64	>64	2	4	>64
V18	64	>64*	>64	>64	>64	1	4	>64
V30	32	64	>64	>64*	>64*	2	2	>64
V31	32	64	>64	>64*	>64*	4	4	>64
V32	32	64	>64	>64*	>64*	2	2	>64
V33	64	64	>64	>64	>64*	2	2	>64
V34	32	32	>64	>64*	>64*	4	4	>64
V62	64	>64*	>64	>64*	>64*	1	16	>64
V63	>64*	>64	>64	>64*	>64	2	32	>64
V64	32	>64	>64	>64*	>64*	2	8	>64
V38	64	>64*	>64	>64	>64	1	4	>64
V40	>64*	>64*	>64	>64*	>64	1	8	>64
V49	16	32	>64*	>64	>64	4	64	>64
V51	16	>64*	>64	>64	>64	8	32	>64
V52	32	32	>64	>64*	>64	4	16	>64
V59	16	64	>64	>64	>64	32	4	>64
V67	16	64	>64	>64	>64	16	8	>64
V68	16	32	>64	>64	>64	8	8	>64
V72	16	32	>64	>64*	>64	8	4	>64
V74	16	64	>64	>64	>64	64	8	>64

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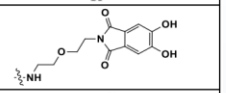
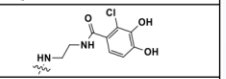
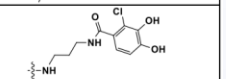
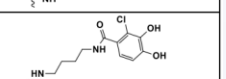
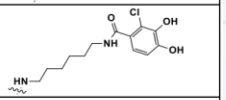
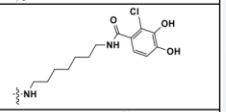
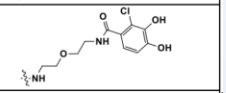
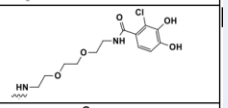
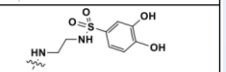
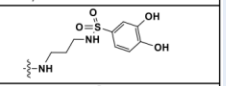
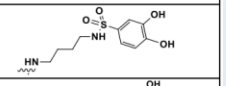
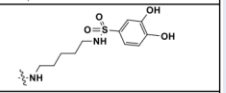
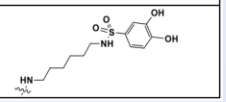
V8	C	
V10	C	
V11	C	
V12	C	
V14	C	
V15	C	
V17	C	
V18	C	
V30	C	
V31	C	
V32	C	
V33	C	
V34	C	

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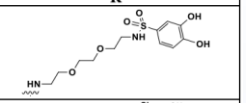
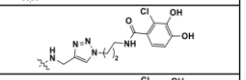
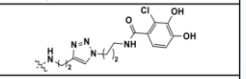
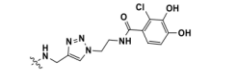
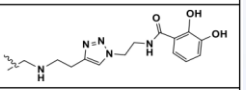
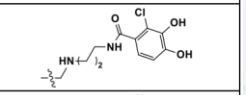
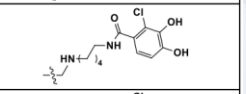
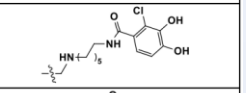
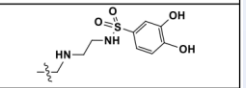
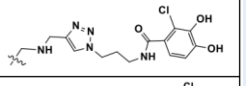
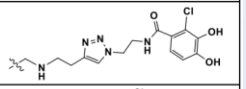
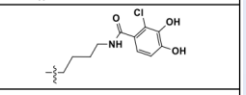
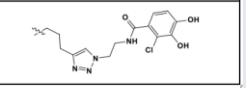
V38	C	
V62	C	
V63	C	
V64	C	
V40	R	
V49	R	
V51	R	
V52	R	
V59	R	
V67	R	
V68	R	
V72	V	
V74	V	

Abbreviations: ACB, A. baumannii JMI #1186154; EC, E. coli (wild-type) BW25113; EC efflux-, E. coli (tolC) JW5503-1; GC, N. gonorrhoeae WHO-Z; KPN, K. pneumoniae ATCC 700603; MW, molecular weight; N/A, not applicable; PSA, P. aeruginosa PAO1; PSA efflux-, P. aeruginosa (multi-pump-gene mutant) PAM1626; SA, S. aureus ATCC 29213.

Solicitation Strategy

- **Phased marketing approach**
  - Initial target: proposal submissions
  - Added donation solicitation
  - Market collection once library established
- **Slow rolled** to avoid project backup
  - Maintain **~20 proposal leads**

- **Initial Submitter Targets**
  - Well-established academic researchers with novel ideas
  - Young academic researchers needing preliminary data
  - Biotechs needing help
  - Entities with contacts within community
- **Extra chemistry resource** for funded academic project

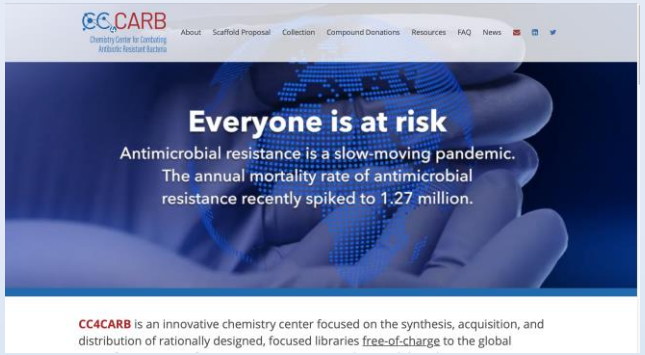
C4CARB
Chemistry Center for Combating Antibiotic Resistant Bacteria

Marketing Tools and Strategy

- **Website:** ***Key tool!*** (www.cc4carb-collection.org):
  - External facing: Marketing/Analytics/Interface
  - Internal facing: Managing program

- **General Marketing:**
  - Social media (Twitter, LinkedIn, etc).
  - Produced logo, emails, newsletter, brochures, presentation.
  - Advertising: LinkedIn, ACS, AMR network affiliations/sponsorship, AAAS

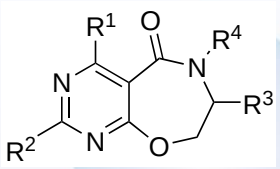
- **Direct Marketing:** Emails, Zoom meetings
  - Academic researchers (publications, grant submissions, websites)
  - Biotechs (websites)
  - AMR support network (Mark Blaskovich, BARDA, etc)
  - AMR community members (conference attendance lists, database searches)



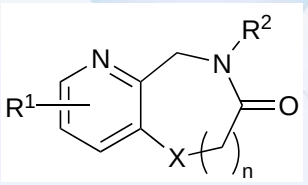
CC4CARB
Chemistry Center for Combating
Antibiotic Resistant Bacteria

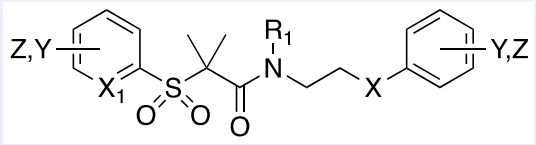
Proposal Observations: In program or via discussions

- Types of **submitters** (out of 32 accepted/in review proposals)
  - 7 Biotech
  - 15 Academic/Institute (including RTI)
  - 3 Donation/Acquisition, 7 NIAID

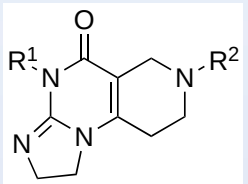


- **Scaffold** types
  - Small molecules
  - Known antimicrobial scaffolds (resistance, broaden activity)
  - Natural products
  - Organometallics
  - Peptides
  - Technology to alter compound properties (penetration, efflux)





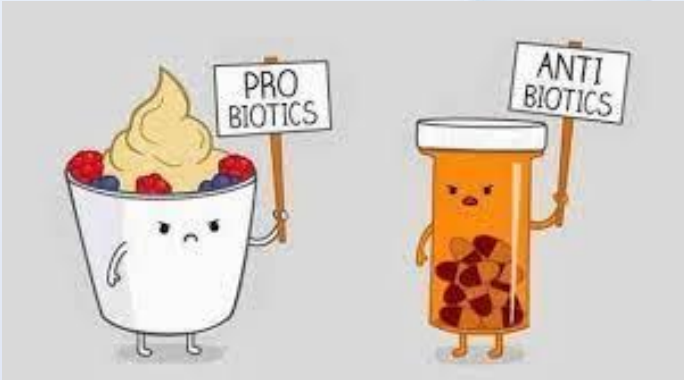
- Scaffold **stage of development**
  - Conceptual (broaden activity, AI, virtual hits)
  - Hit to Lead
  - Mature projects needing tweaking/SAR



- Proposals/ideas **difficult to fund elsewhere** or **difficult to synthesize**

Proposal Observations: In program or via discussions

- **Gram-negative** area
  - Improve/broaden activity of known or novel scaffold
  - Selective Gram-negative activity
  - Efflux pump inhibitors
  - Novel penetration technology applied to existing antibiotics
- Interest in **other areas**
  - High interest in TB
  - Increasing interest in nontuberculous mycobacteria
  - Queries about anti-fungal testing



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Chemistry Center for Combating Antibiotic Resistant Bacteria

Thank you

CC4CARB

Chemistry Center for Combating Antibiotic Resistant Bacteria

Bruce Blough – Principal Investigator
Elliott Pauli – Solicitation Manager

www.cc4carb-collection.org

Toll-free: (833)-870-0484

CC4CARB@rti.org

NIAID: Jeremy Starr (jeremy.starr@nih.gov)
Rick Sciotti (rick.sciotti@nih.gov)

Gerry Wright

Gerard (Gerry) Wright is a Professor in the Michael G. DeGroote Institute for Infectious Disease Research and the Department of Biochemistry and Biomedical Sciences and holds the Michael G. DeGroote Chair in Infection and Anti-Infective Research at McMaster University.

He was elected as a Fellow of the Royal Society of Canada and a fellow of the American Academy of Microbiology and is the recipient of a Killam Research Fellowship, Murray Award for Career Achievement of the Canadian Society of Microbiologists among other awards.

He has trained over 75 graduate students and postdocs and is the author of over 300 manuscripts. His research interests are in the origins and mechanisms of antibiotic resistance in the clinic and the environment and the discovery of new anti-infective strategies, focusing on the application of microbial natural products and synthetic biology towards this goal.

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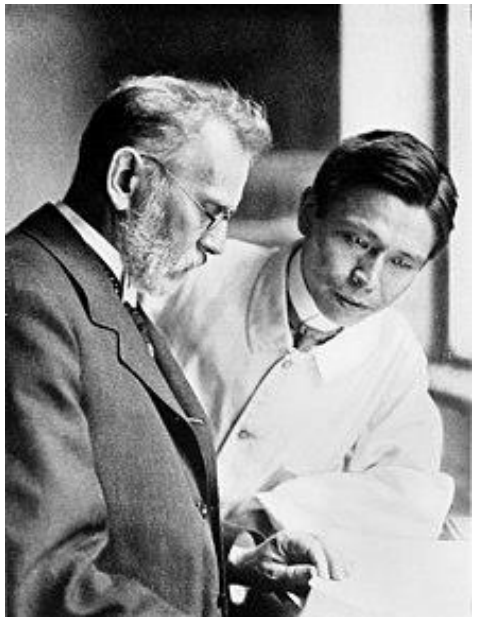
Antibiotic Screening Campaigns

Gerry Wright

Michael G. DeGroote
INSTITUTE FOR INFECTIOUS DISEASE RESEARCH

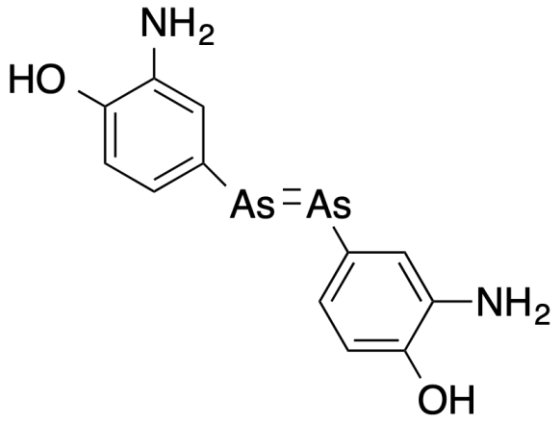
David Braley Centre
for Antibiotic Discovery

The 1st 'screen'



Paul Ehrlich & Sahachiro Hata

Salvarsan
Compound 606
"Magic Bullet"
1910



Mice, guinea pigs, rabbits infected with
Treponema pallidum

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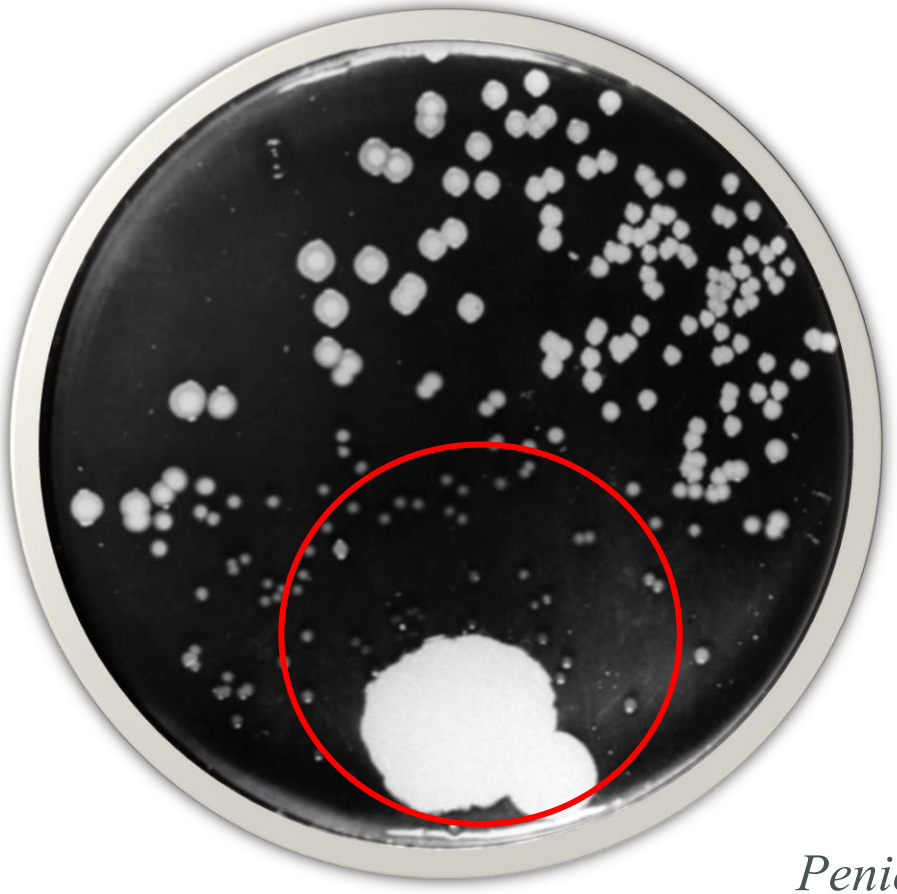
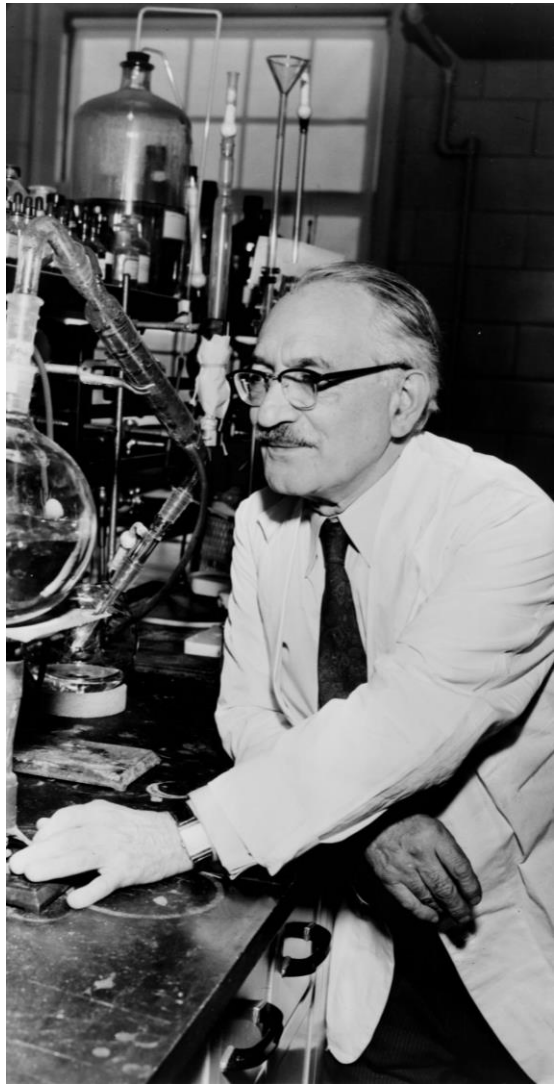
The first *in vitro* 'screen'

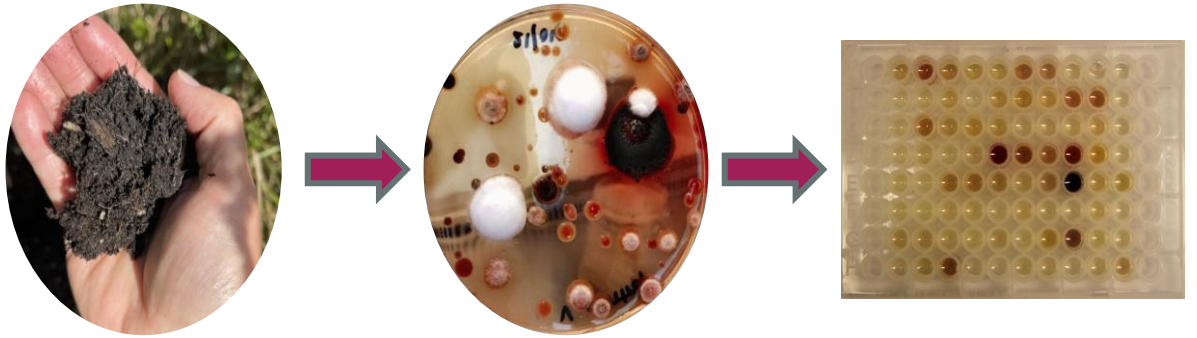


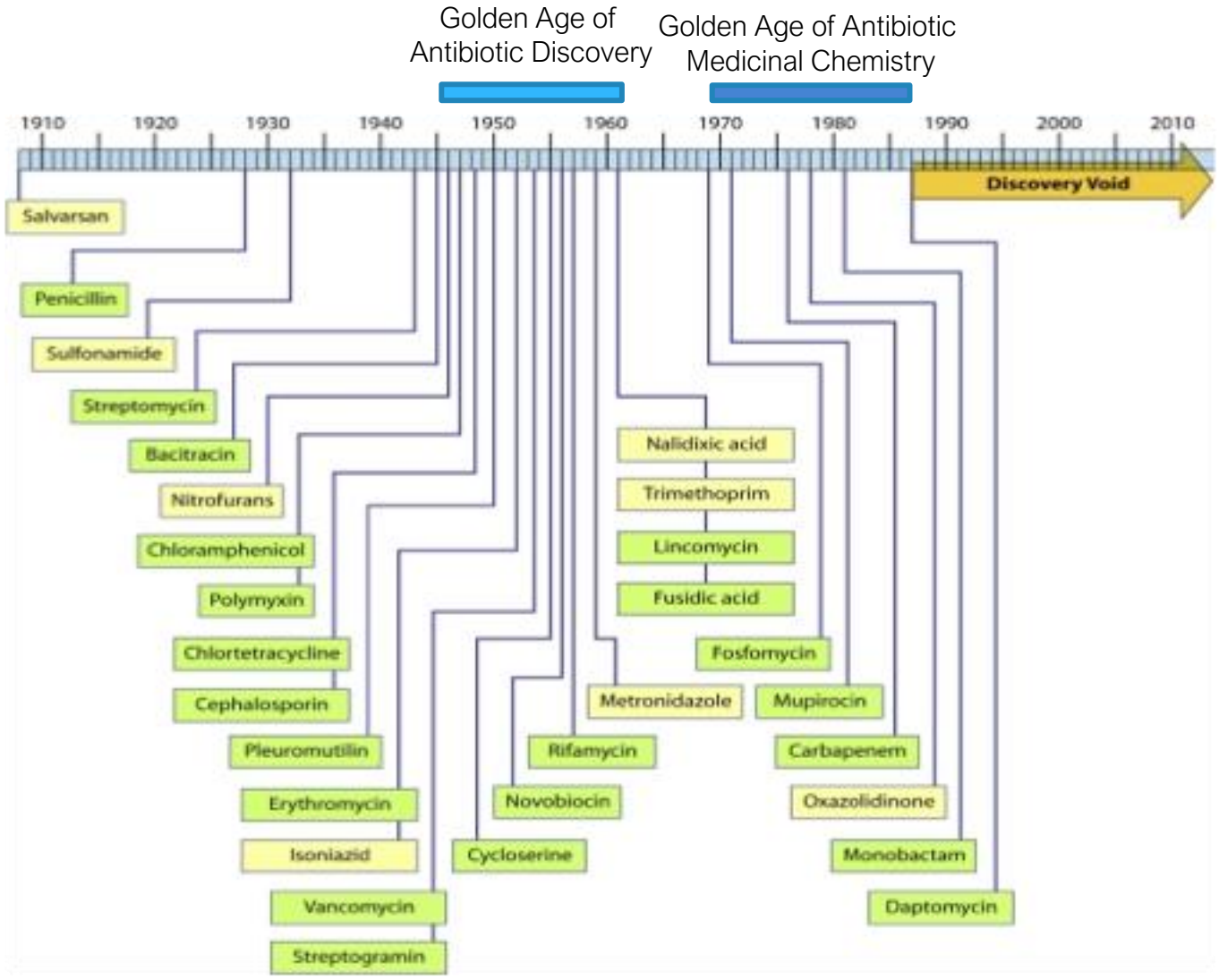
Penicillium notatum, 1928



The Waksman Platform – Cell Killing Phenotype

- Purify and culture environmental (soil) microbes (Actinomycetes, fungi)
- Prepare extracts
- Test susceptible bacteria cells for growth inhibition
- While this approach was first used using extracts of compounds produced by microbes, it can also be used with libraries of synthetic chemicals





Lynne Silver *Clin Microbiol Rev* (2011) **24:**71-109

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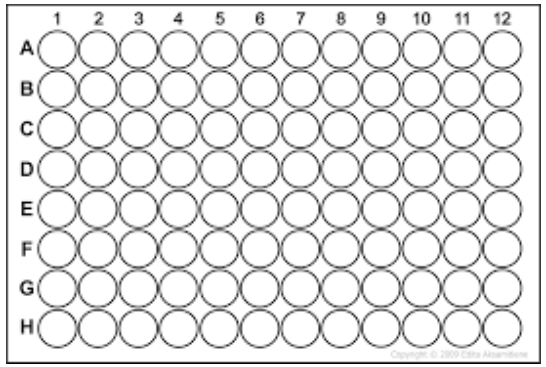
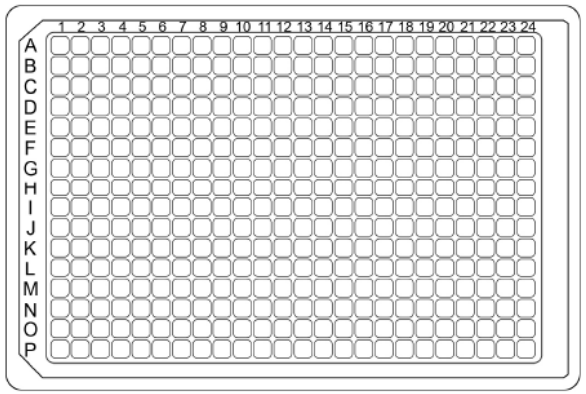
High Throughput Whole Cell Screens (WCSs)

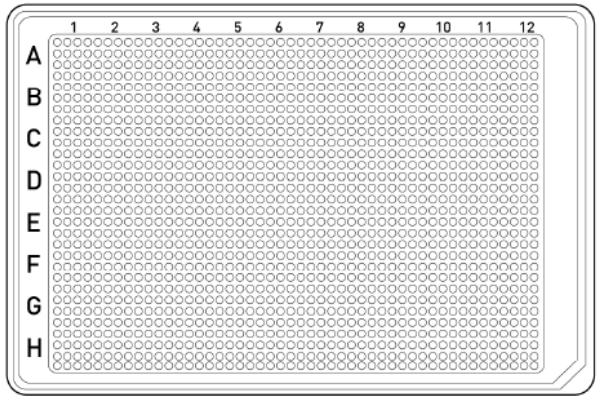
Microtitre Plates



96



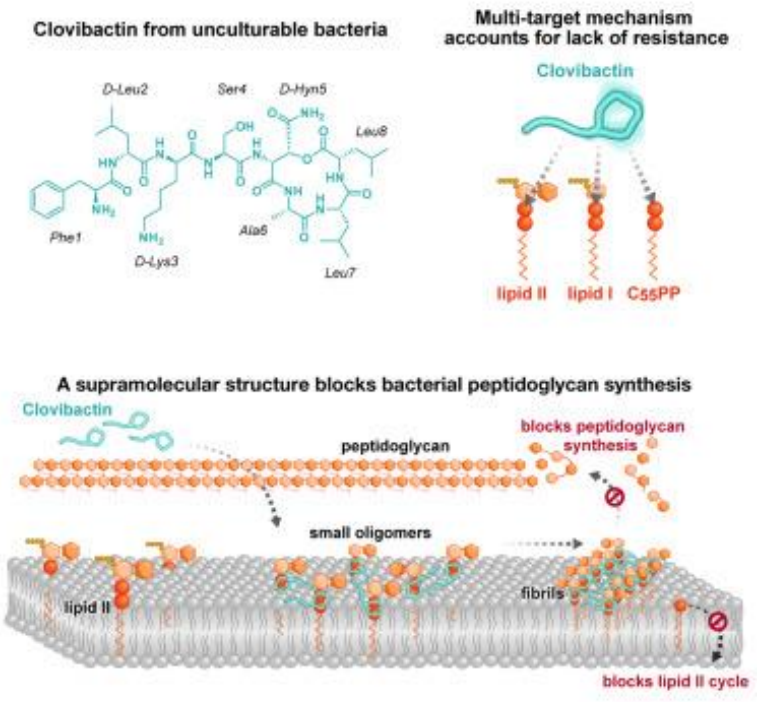
384



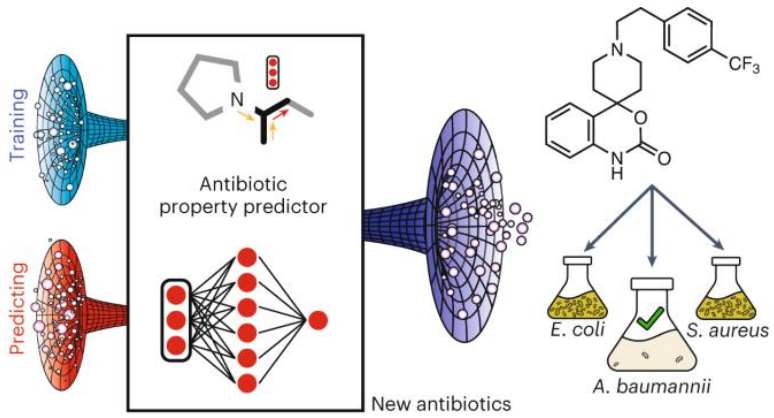
1536

1. Add compounds
2. Add liquid media (e.g. MHB)
3. Add organism
4. Incubate
5. Assay (OD600 nm, Fluorescence e.g. GFP, Luminescence, etc.)
6. Variation: solid agar impregnated with target bacteria and pin compounds

WCSs continue to uncover new antibiotics



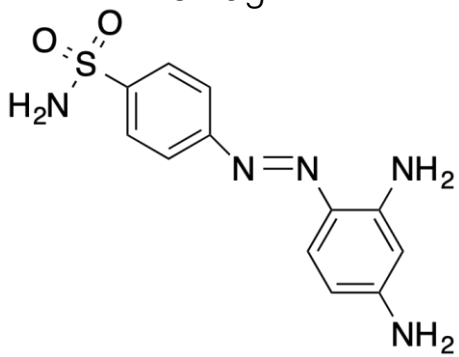
Cell 2023 https://doi.org/10.1016/j.cell.2023.07.038



Nature Chem Biol (2023)
https://doi.org/10.1038/s41589-023-01349-8

Antimetabolites and Virulence Factors

Gerhard Domagk



Protonsil
1931

- WCSs are often conducted in rich media
- This misses antimetabolites or compounds that may inhibit virulence factors or targets that are essential for growth in an infection

- Screen in minimal media
- Screen under more physiologic conditions e.g. artificial urine, serum

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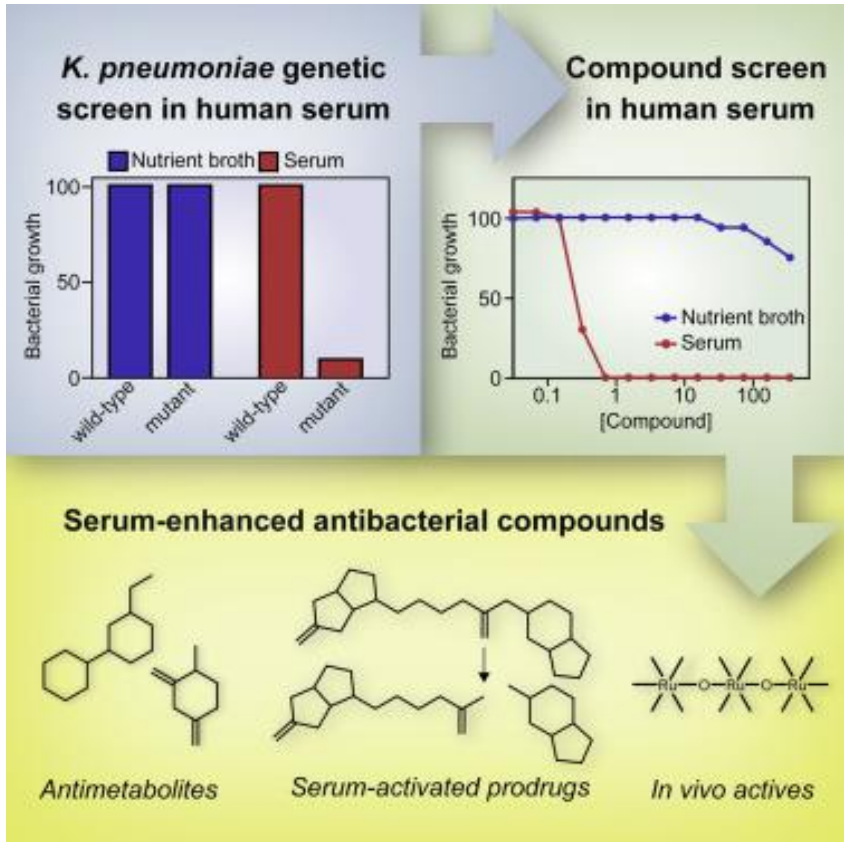
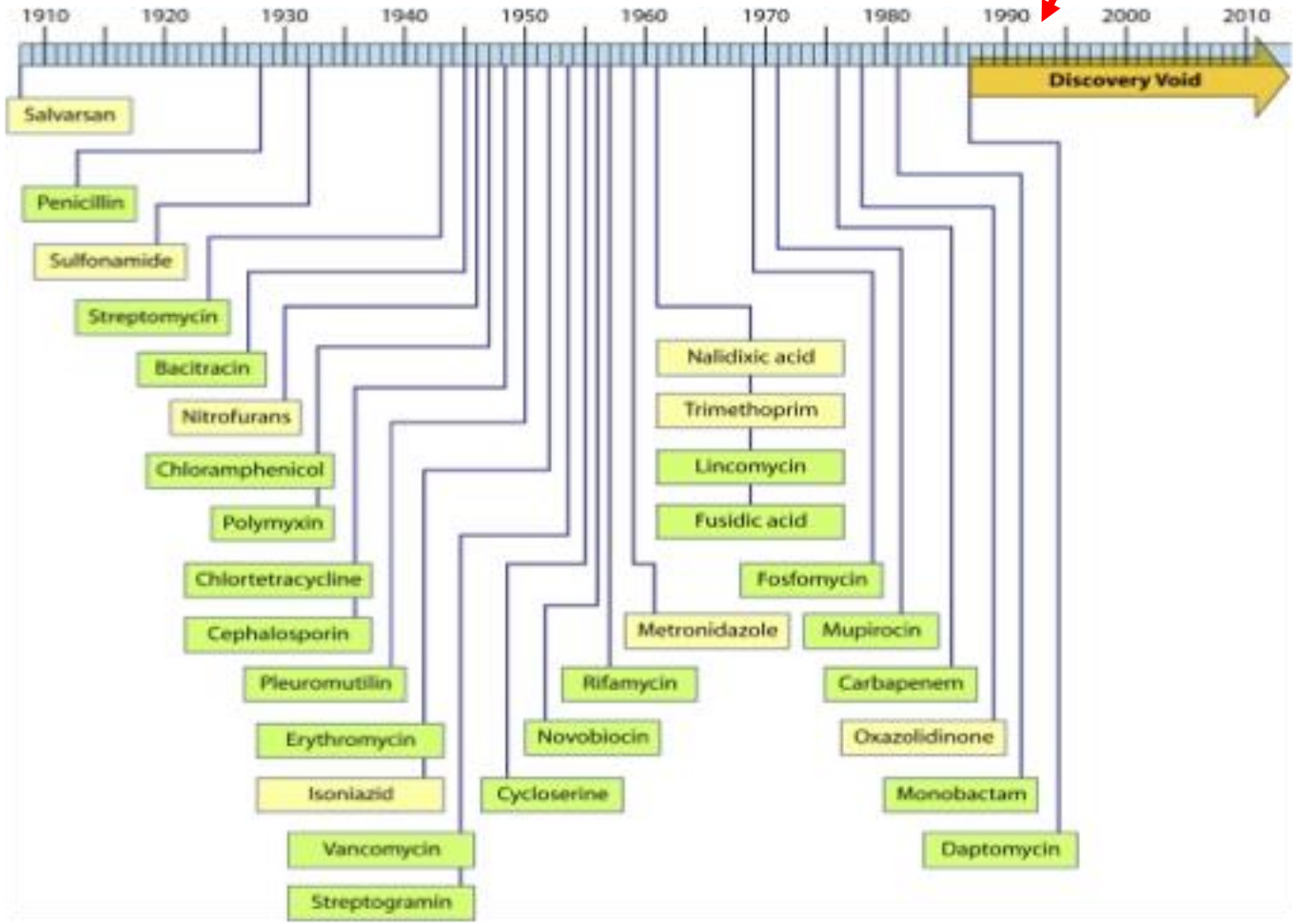
Klebsiella pneumoniae screen in human serum



Cell Reports (2020) **3**:107927

1st Whole genome sequencing
Combinatorial Chemistry
Advances in protein structure determination



Lynne Silver *Clin Microbiol Rev* (2011) **24:**71-109

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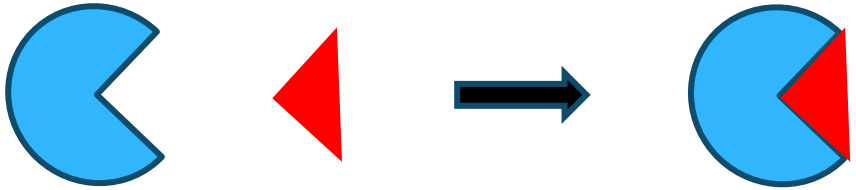
In vitro Target-based Screens



- WCSs of natural products did not yield many new antibiotic leads after the 1970s
- New technology ushered in the era of in vitro Target Based Screens (TBSs)
- Purified “essential” proteins or receptors screened in HT
- Most pharma pivoted to this approach
- GSK 70 screens 1995-2001 no candidate drugs (*Nat Rev Drug Discovery* 2007 **6**:29)
- Astra 65 screens 2001-2010 no candidate drugs (*Nat Rev Drug Discovery* 2015 **14**:529)

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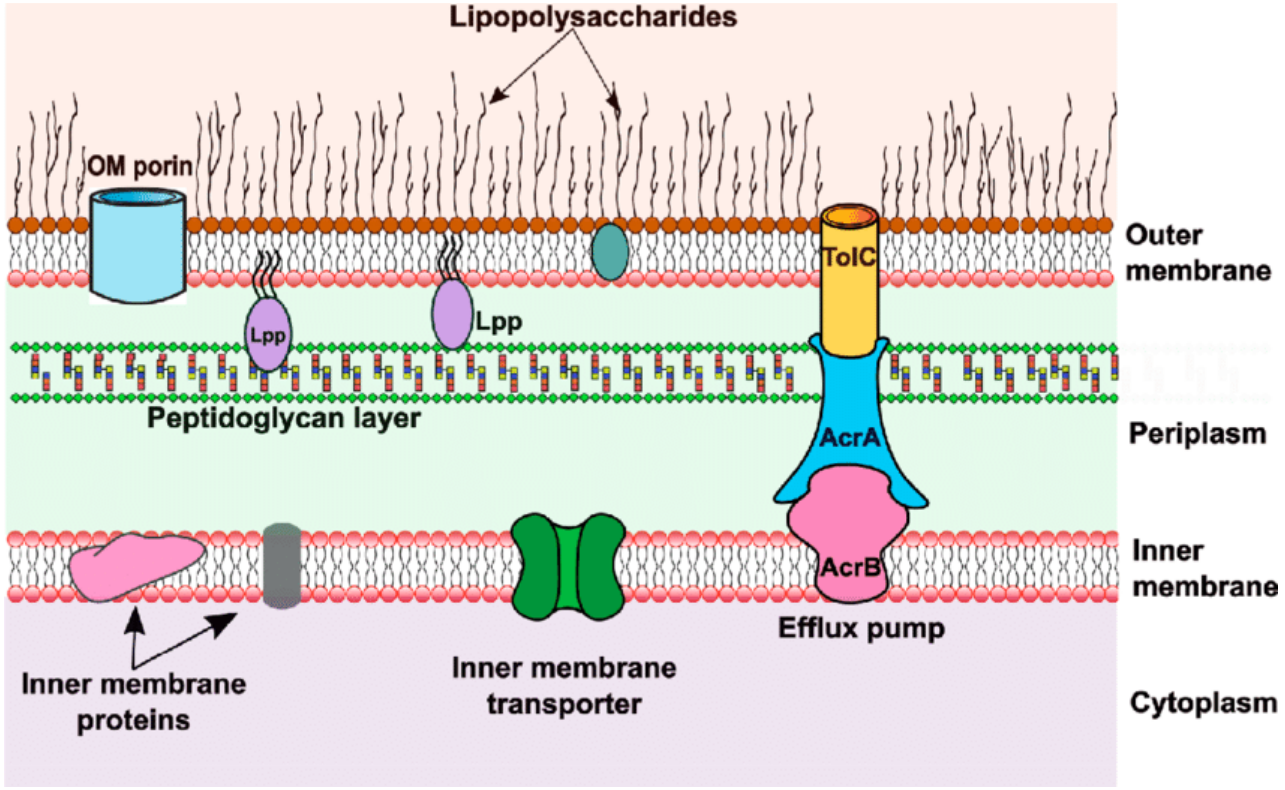
Why?



- Physical properties of cell penetrating compounds are complex in bacteria
- Chemical libraries
- Successful antibiotics are tough to beat

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TBS vs WCS

Pros

- Allows focus on target up front in campaign
- Rapid cycles of SAR and target engagement to get to better inhibitors or tighter binders

Cons

- No guarantee of whole cell activity
- Poor track record

Pros

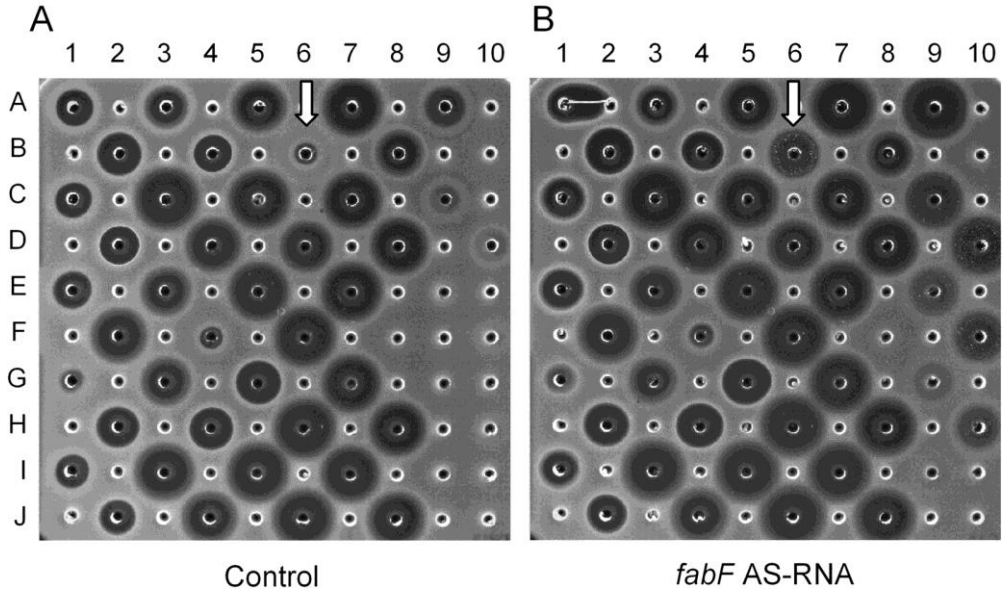
- Actives are, by definition, bioactive
- Great track record

Cons

- Needs additional work to identify target
- Might not be a target that is easily biochemically assayed

Combining TBSs and WCSs

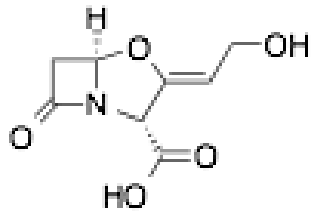
- Decrease titer of essential gene products e.g., by control with a regulatable promoter or expressing antisense RNA
- E.g. discovery of fatty acid synthesis inhibitors



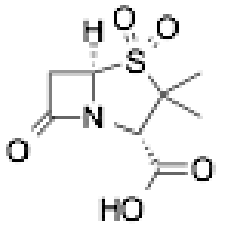
Antimicrob. Agents Chemother. (2006) **50**: 519

Resistance as a 'Target'

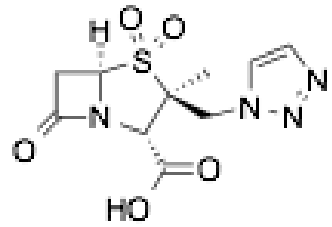
- β-lactamase inhibitors
- several in clinic, many more n development
- Efflux inhibitors
- Others



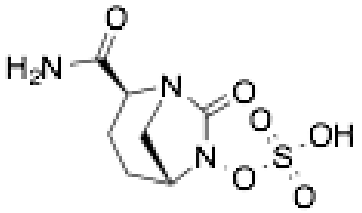
Clavulanic Acid



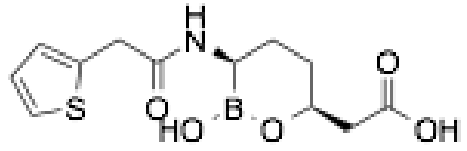
Sulbactam



Tazobactam



Avibactam



Vaborbactam

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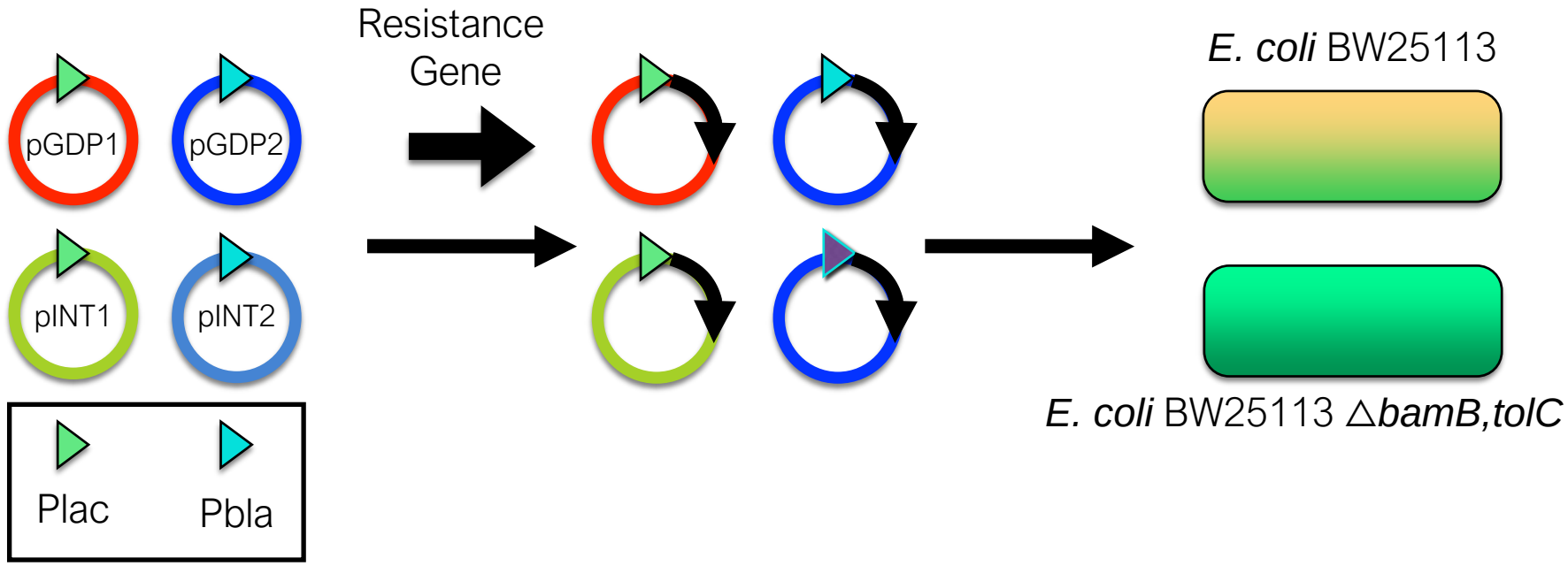
ARP: Platform for Antibiotic Dereplication/Liability and for Screening for Inhibitors of Resistance



Cell Chem Biol (2017) **24**:98-109

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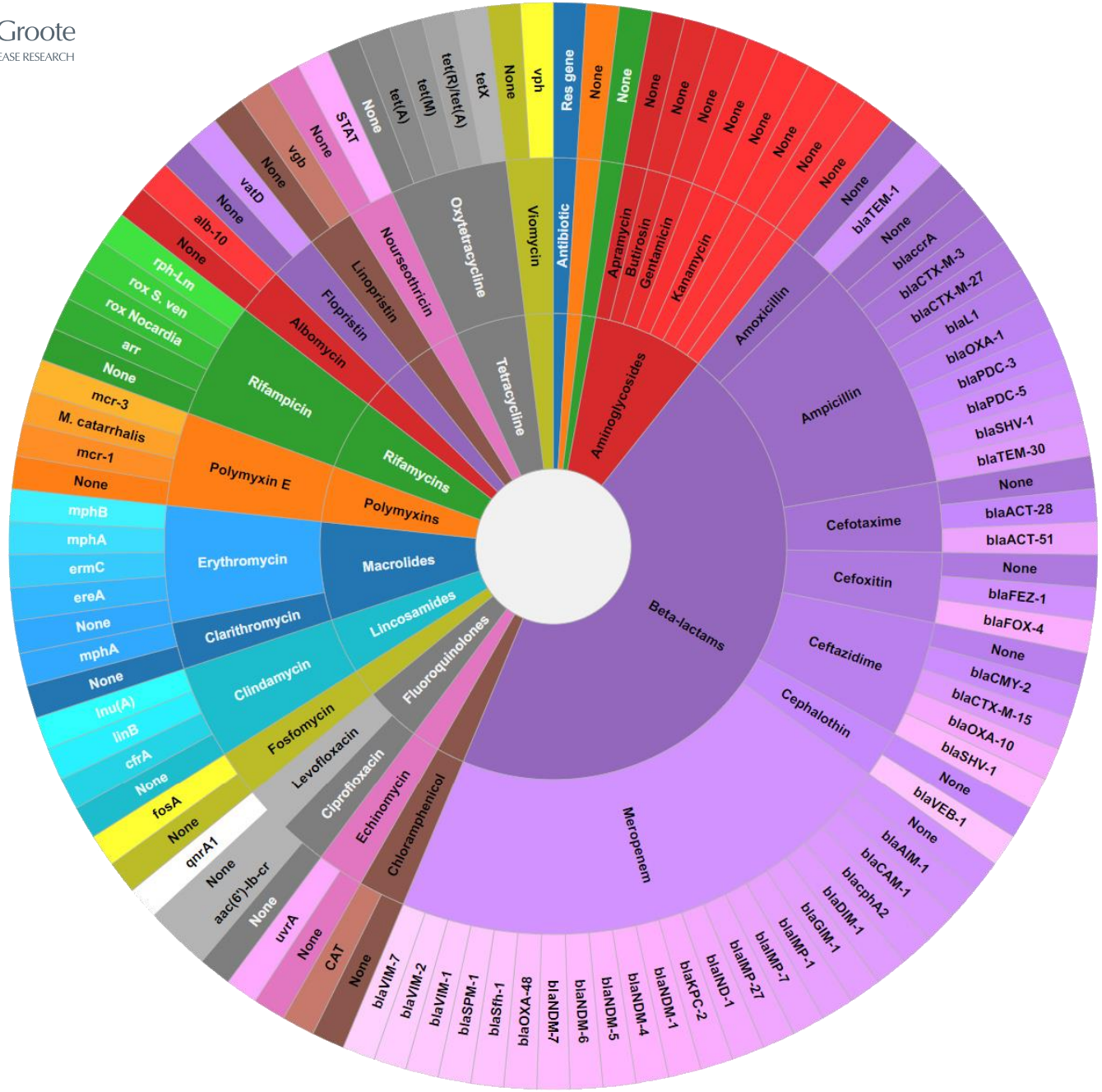
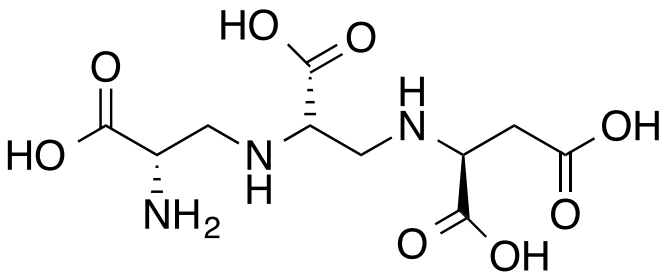


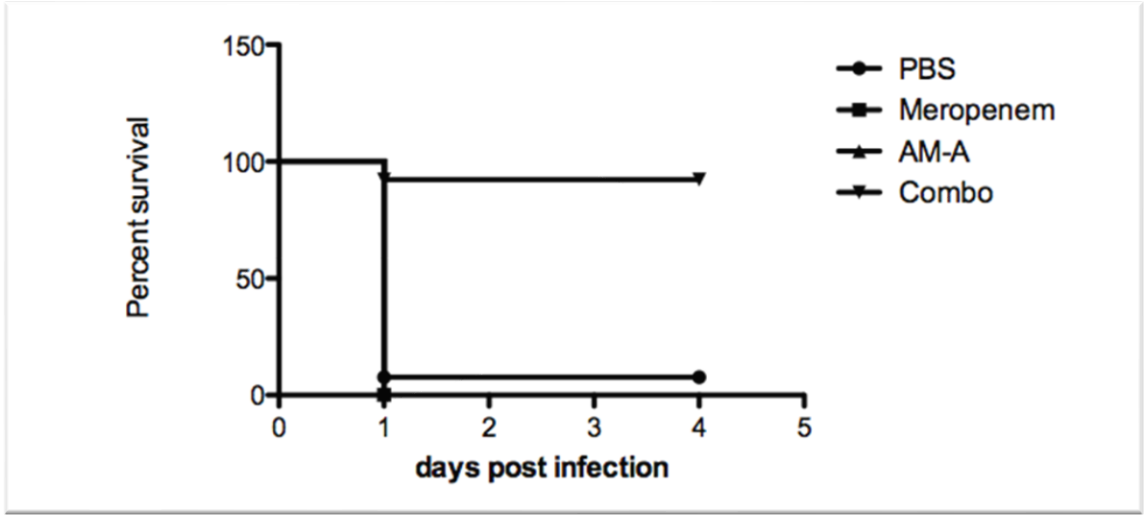
https://www.thewrightlab.com/antibiotic-resistance-platform

AMA – metallo-beta-lactamase inhibitor

- WCS of *E. coli* expressing NDM-1 natural product extracts in the presence of meropenem



AMA (aspergillomarasmine A)

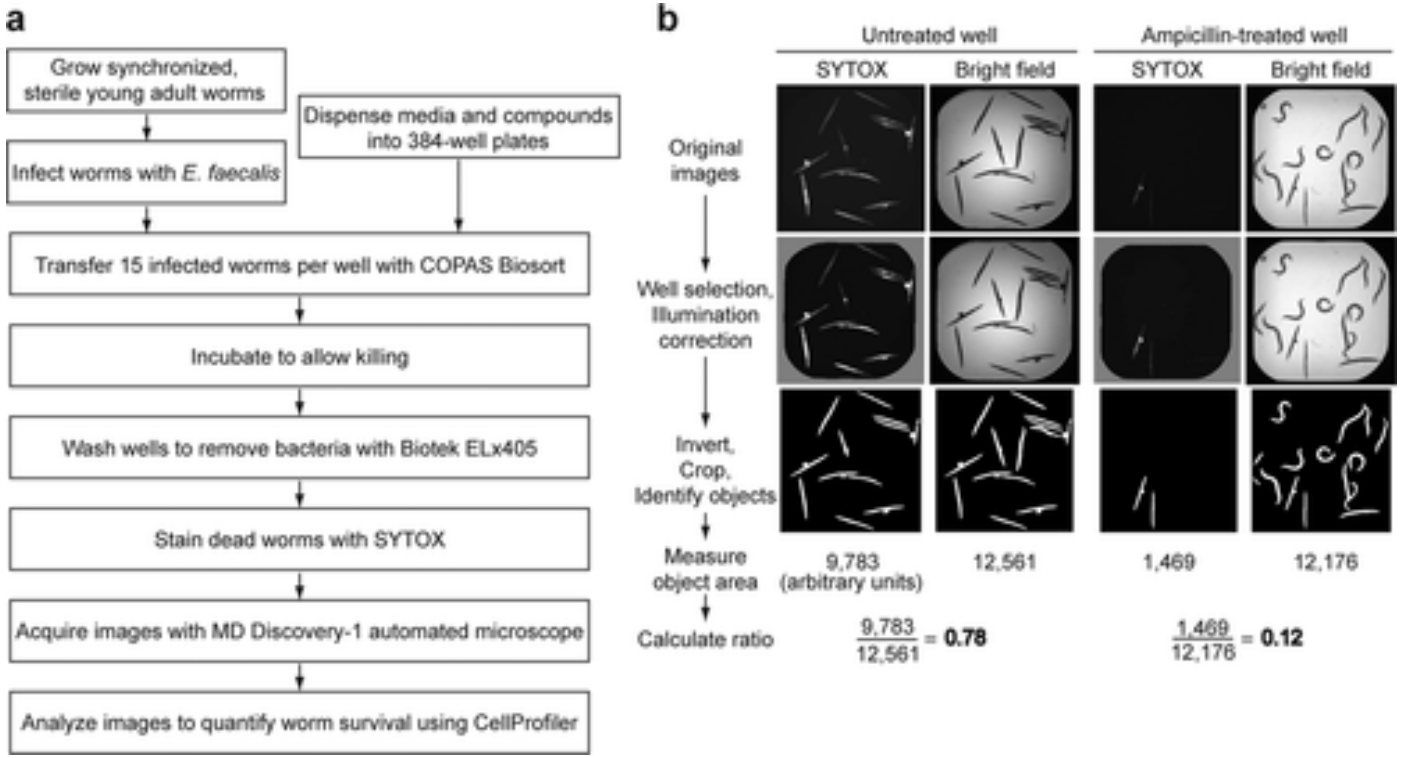


***Klebsiella pneumoniae* IP**

Nature (2014) **510**:503-06

In vivo Screens

- WCSs in an infected model organism (Erlich and Domagk)
- Can be HT e.g. *C. elegans* infected with *Enterococcus faecalis*



ACS Chem Biol (2009) **4:**527

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Summary

- WCSs and TBSs each have their advantages and disadvantages
- In vivo TBSs have not yet yielded new antibiotics
- Creatively combining TB and WC screens offers an opportunity for innovation

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Acknowledgements

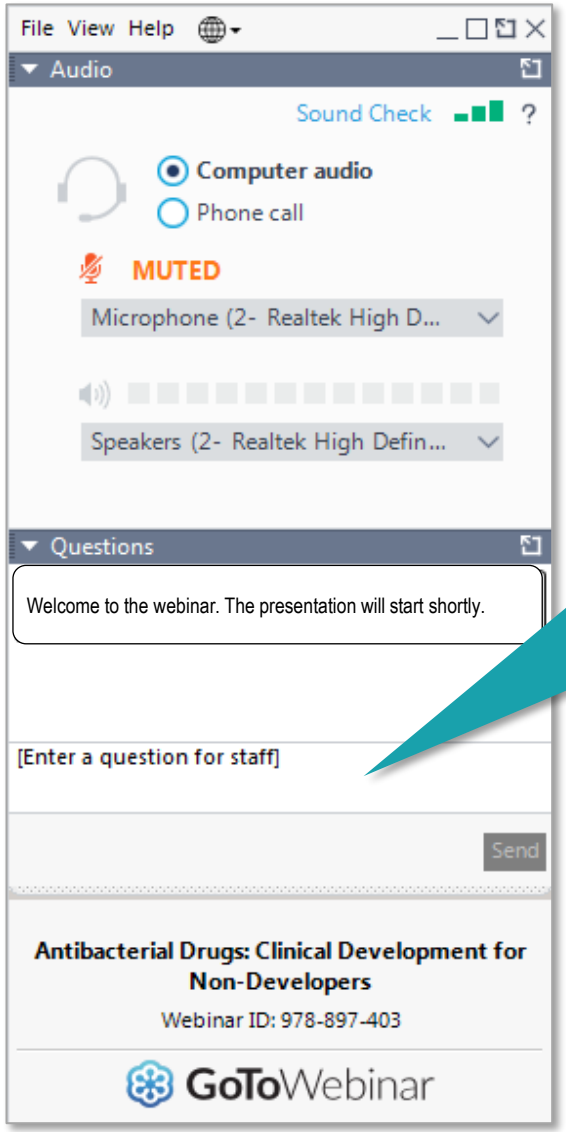
www.thewrightlab.com
@gerryiidr

Ontario Research Fund

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

Starting an antibacterial drug discovery screening programme

Bruce Blough
Principal Investigator and Senior Research Chemist
Chemistry Center for Combating Antibiotic Resistant Bacteria – CC4CARB
& RTI International (USA)

Gerry Wright
Professor
DeGroote Institute for Infectious Disease Research, McMaster University (Canada)

Moderator:
Philip Gribbon
Head of Discovery Research
Fraunhofer Institute for Translational Medicine and Pharmacology – ITMP (Germany)

Upcoming webinars

In collaboration with: ecraid

Clinical trials platforms for new and neglected antimicrobials

With Jesús Rodríguez-Baño & Julia Bielicki

20 September 2023, 11:00-12:30 CEST

Antibiotic shortages: causes, consequences, and solutions

With Esmita Charani, Jennifer Cohn, Kopano Klaas & Chaitanya Koduri

27 September 2023, 14:00-15:00 CEST

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