

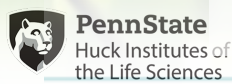
# New Frontiers of Natural Products

## SURF Users Association Meeting

Josh Kellogg, Ph.D.

Pennsylvania State University

October 26, 2022



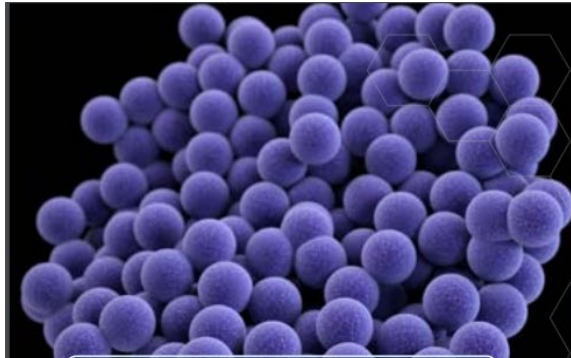


# An Emerging Crisis

## Millions are dying from drug-resistant infections, global report says

By Philippa Roxby  
Health reporter

19 hours ago



### METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

**80,461** SEVERE MRSA INFECTIONS PER YEAR

STAPH BACTERIA ARE A LEADING CAUSE OF HEALTHCARE-ASSOCIATED INFECTIONS

THREAT LEVEL **SERIOUS**

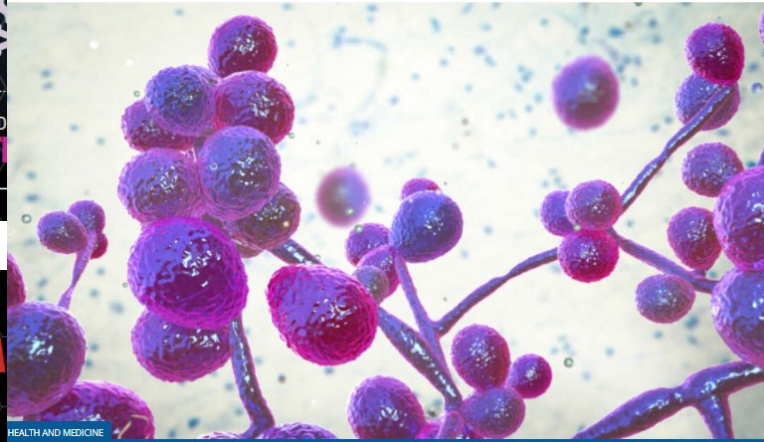
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

### Outbreak Of Notorious "Superbug" Fungus Emerges In US Hospital

17.1K SHARES

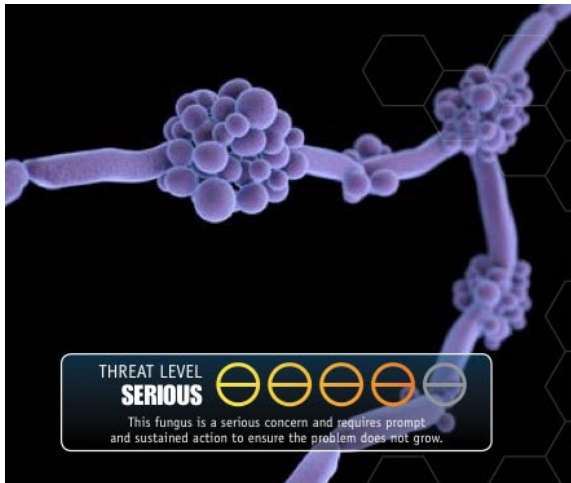
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Share on Twitter



GETTY IMAGES

Antibiotics may no longer work because the bacteria they are intended to kill is becoming resistant



### FLUCONAZOLE-RESISTANT CANDIDA

**3,400** FLUCONAZOLE-RESISTANT CANDIDA INFECTIONS

**220** DEATHS

**46,000** CANDIDA INFECTIONS PER YEAR

THREAT LEVEL **SERIOUS**

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

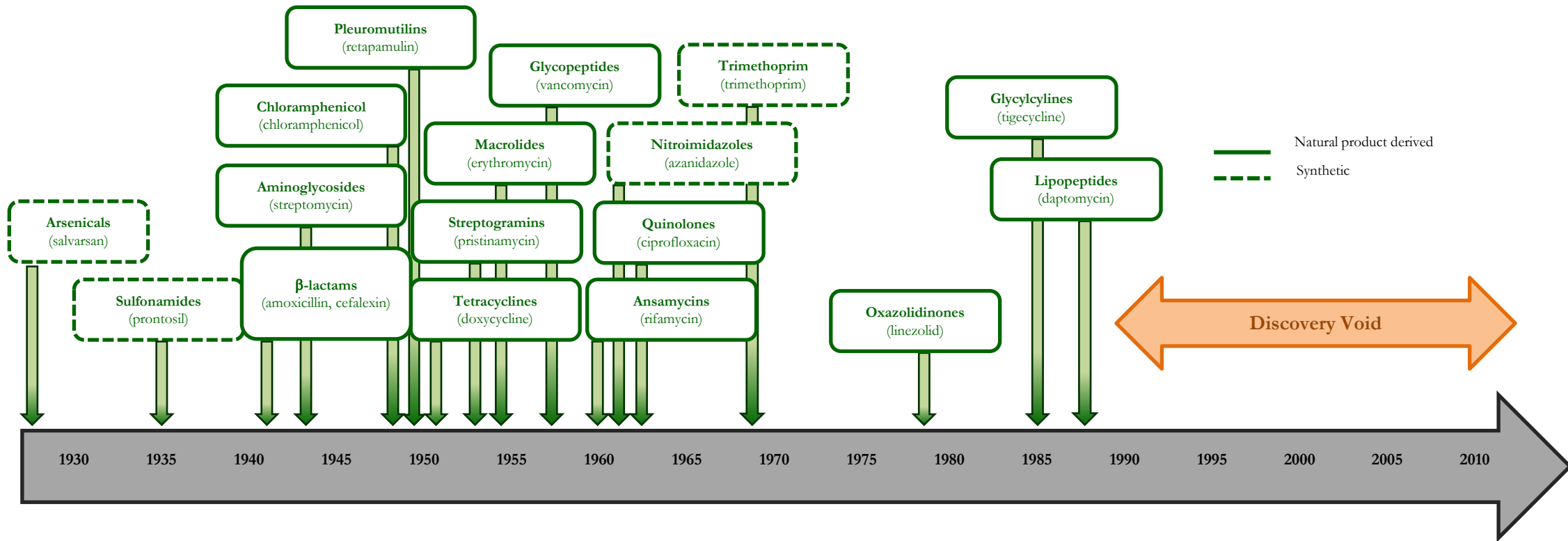
**NEW TREATMENTS ARE OF IMMEDIATE CONCERN!**

*"The world is heading towards a post-antibiotic era, in which many common infections will no longer have a cure and, once again, kill unabated."*



WHO Director General  
Dr. Margaret Chan

# Slowed Development



# 'Neglected' Tropical Diseases

## Helminth NTDs

Taeniasis/Cysticercosis  
Guinea worm disease  
Echinococcosis  
Foodborne trematodiasis  
Lymphatic filariasis  
Soil-transmitted helminthiasis  
Schistosomiasis  
Onchocerciasis

## Viral NTDs

Rabies  
Dengue  
Chikungunya

## Bacterial NTDs

Leprosy  
Trachoma  
Yaws  
Buruli Ulcer

## Protozoan NTDs

Chagas disease  
Leishmaniasis  
Human African  
trypanosomiasis

## Fungal NTDs

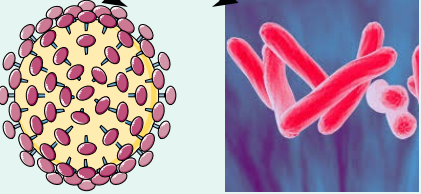
Mycetoma  
Chromoblastomycosis  
Others..

## Ectoparasitic NTDs

Scabies  
Others...



# Synergy



# Ethnobotany

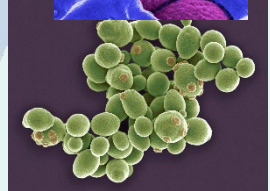
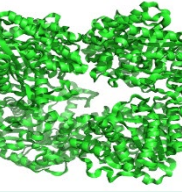
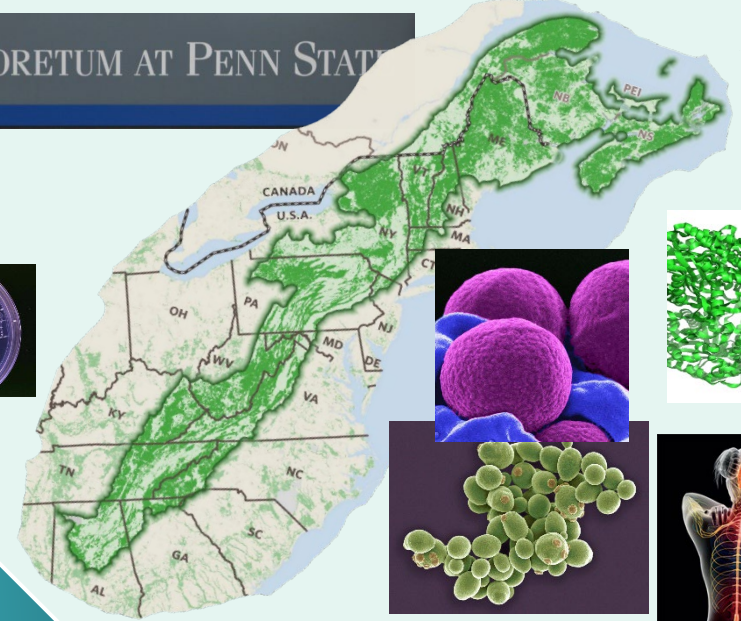


Broad Research Themes (thus far...)

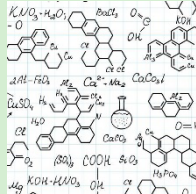
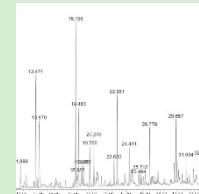
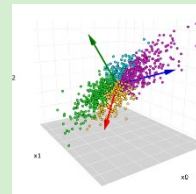
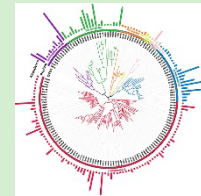
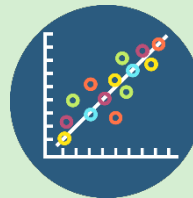
# Natural Product Discovery



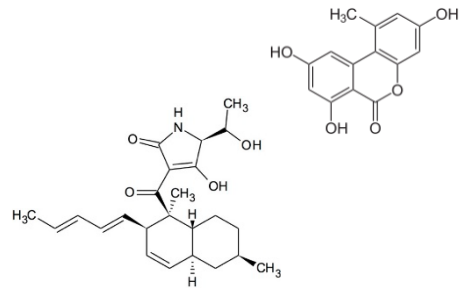
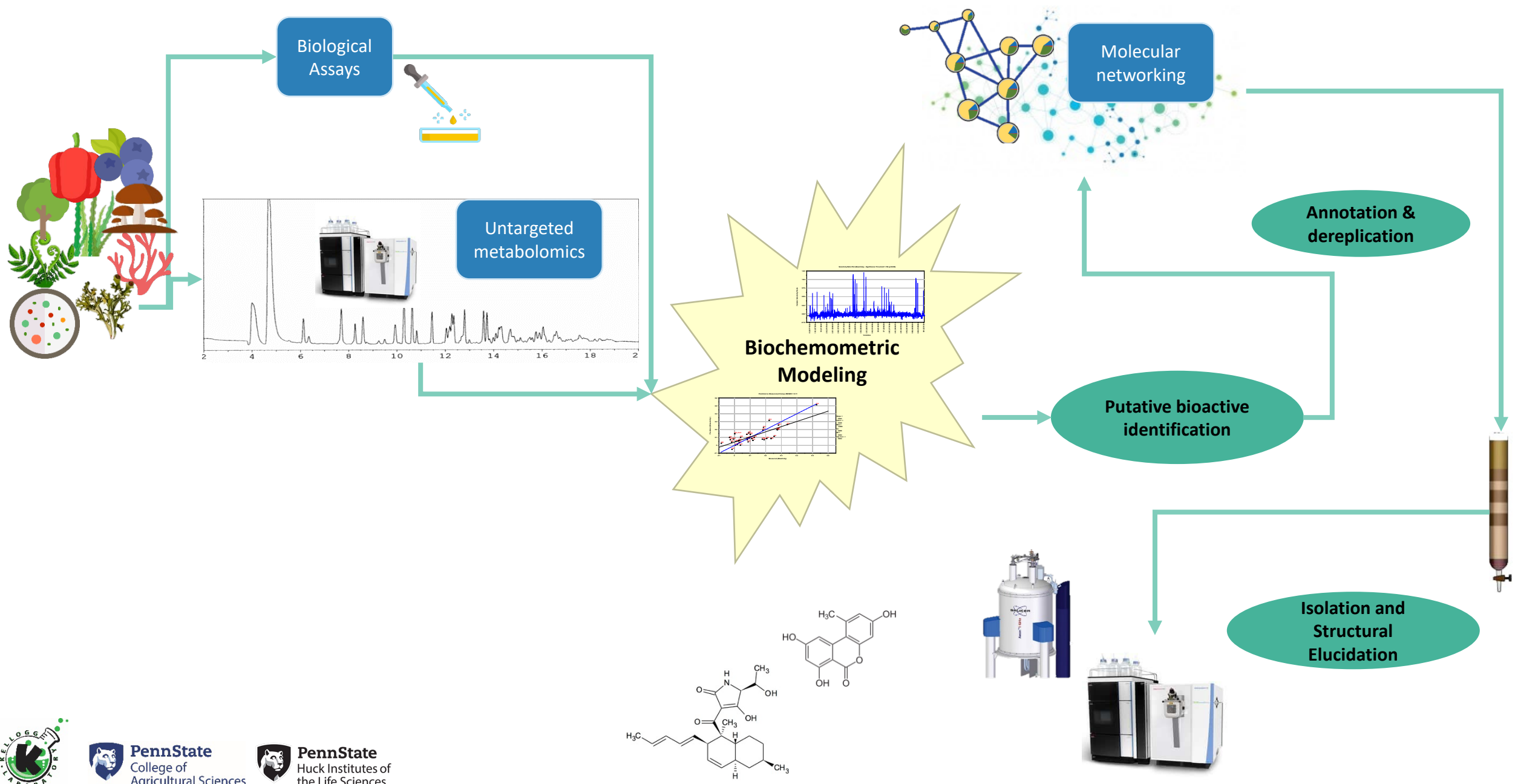
THE ARBORETUM AT PENN STATE



# Analytical Metabolomics



# Biochemometrics

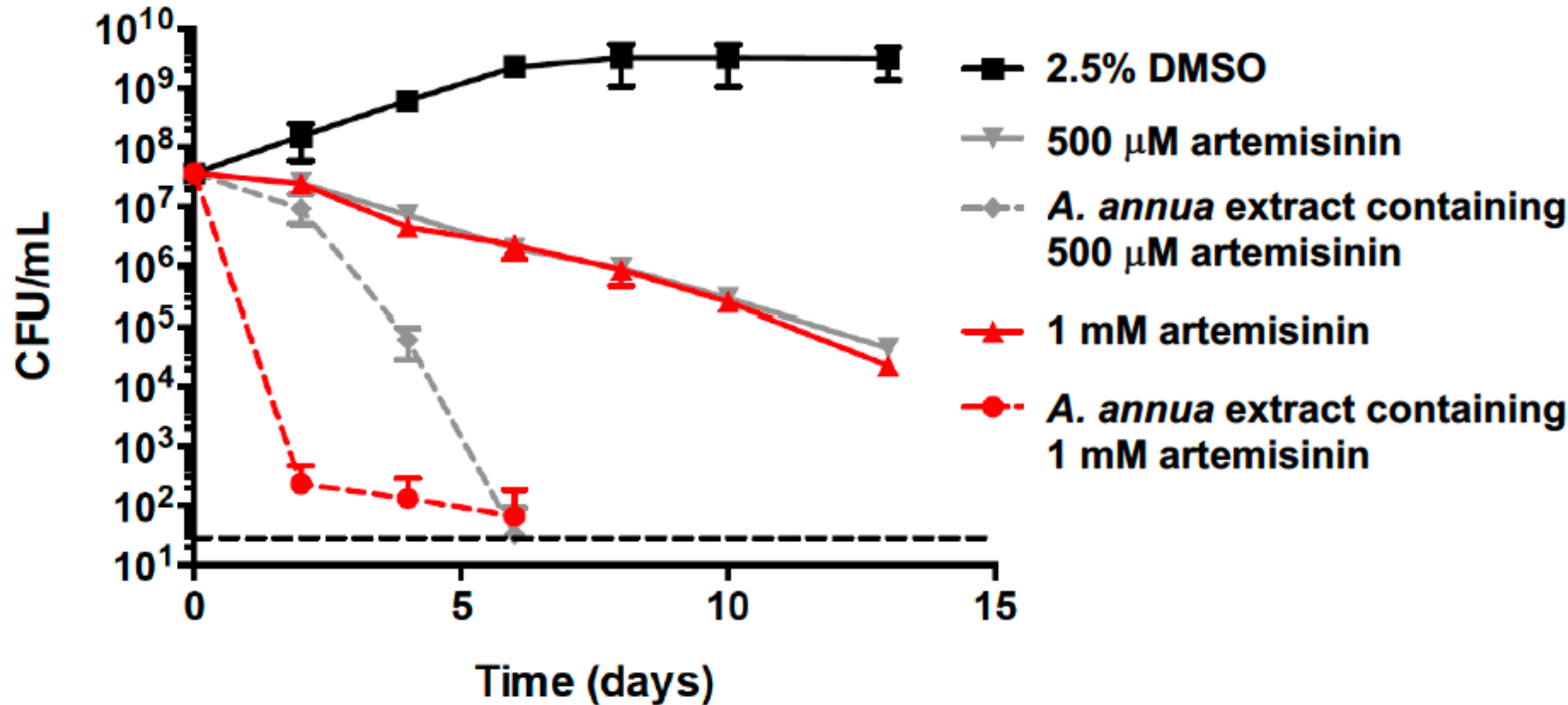
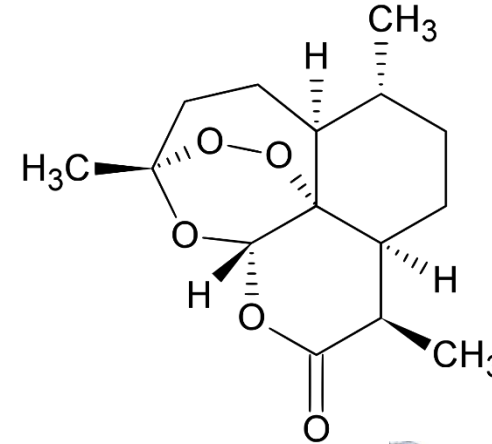




# Artemisia – more than just malaria



<https://elifesciences.org/digests/41129/tuberculosis>  
<https://www.medicaldevice-network.com/news/tuberculosis-bacteria-thrive-on-a-nitrogen-source-buffet-blood-test/>



<https://fineartamerica.com/featured/sweet-annie-artemisia-annua-gregory-g-dimijian-md.html?product=poster>



# Bioactive Ligands from TCM Sources

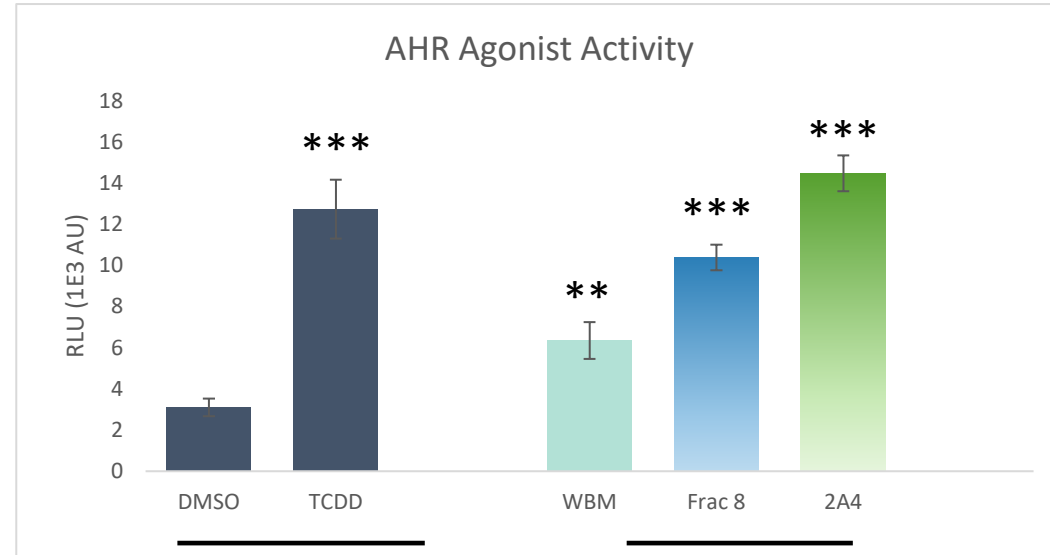
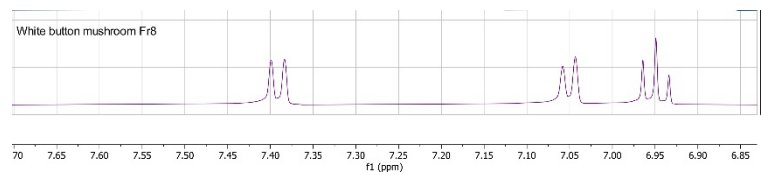
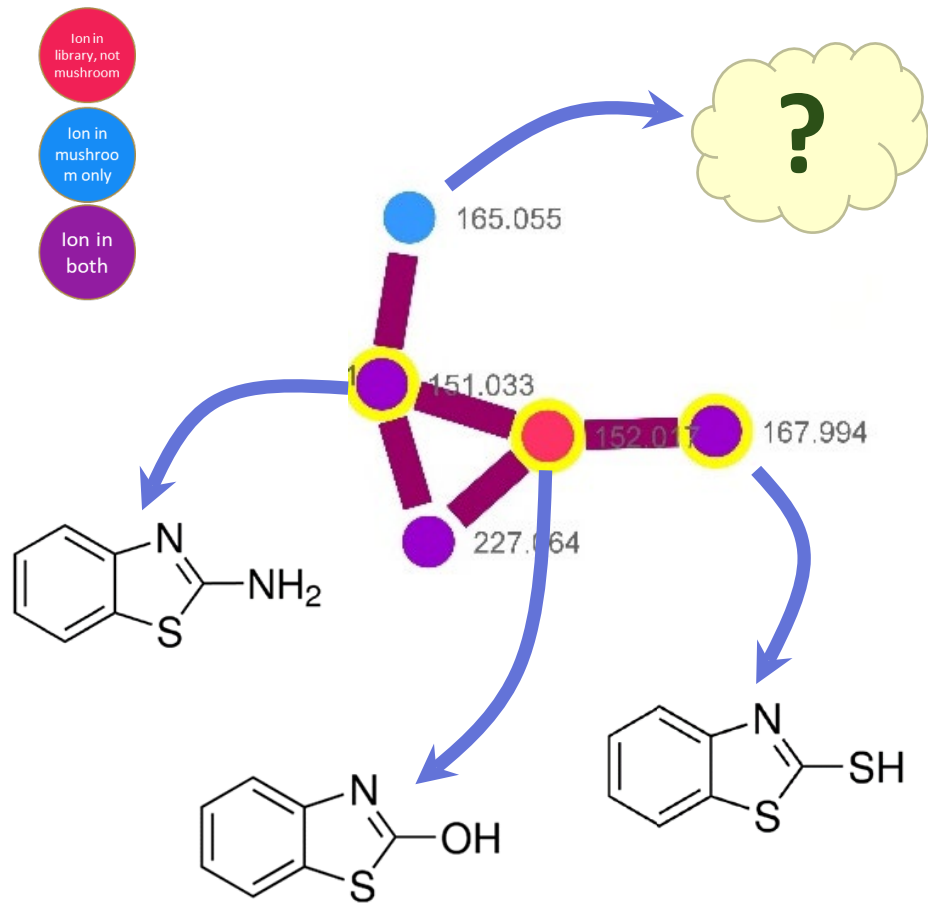


**Ban Xia**  
**Xie Xin Tang**  
**Liu Jun Zi Tang**  
**Shao Yao Gan Cao Tang**  
**Gui Zhi Jia Shao Yao Tang**  
**Yi Zi Tang**  
**Ma Zi Ren Wan**





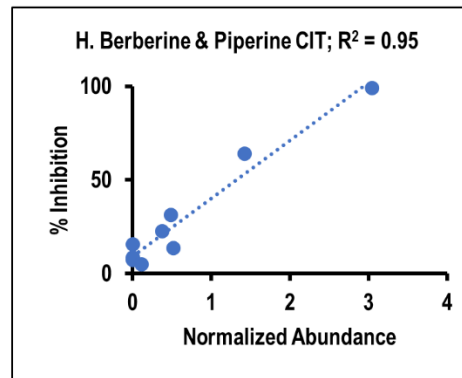
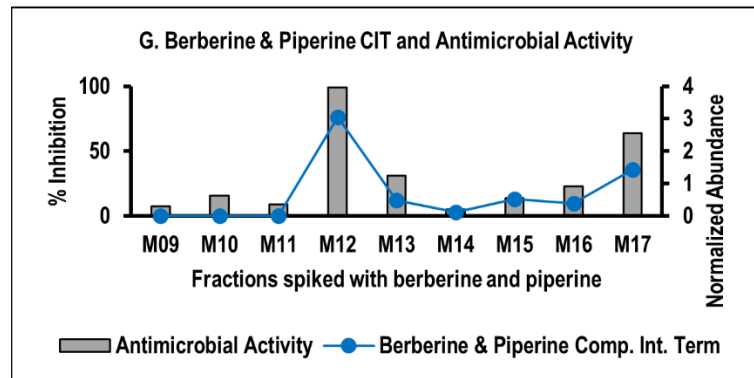
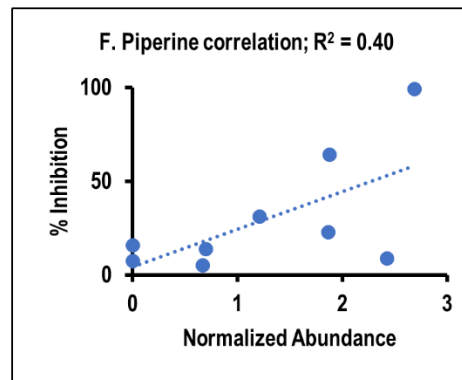
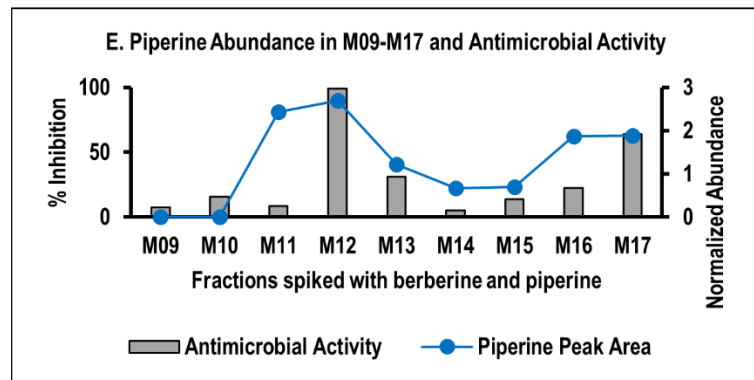
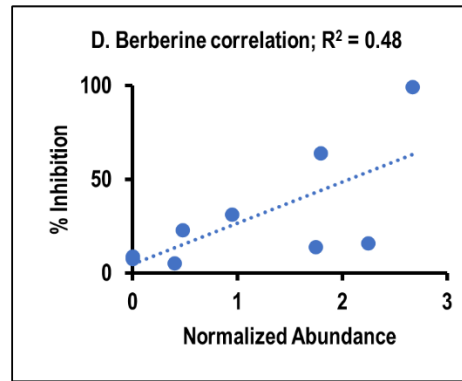
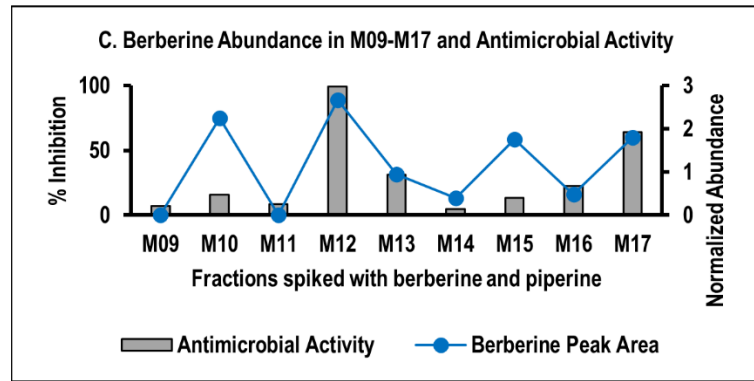
# Mining the Network



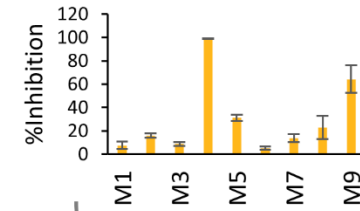
\* - vs control  
 \*\* p<0.01  
 \*\*\* p<0.001



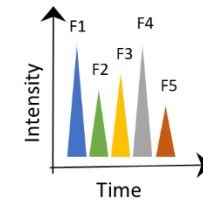
# Combination Modeling for Synergists



## Biological Activity Data

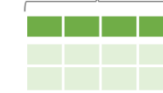


## Metabolomics Data

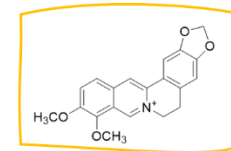


### A. Classical Metabolomics

data matrix



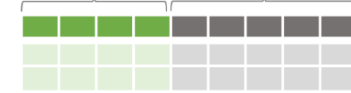
Data Normalization and Statistical Analysis



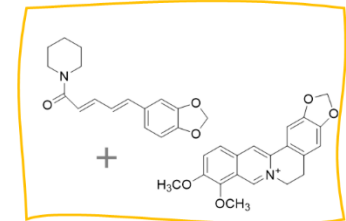
**Putative Active(s)**

### B. Interaction Metabolomics

data matrix + compound interaction terms (CIT)



Data Normalization and Statistical Analysis



**Putative Synergists**





Where will  
the next  
generation of  
bioactive  
molecules  
come from?





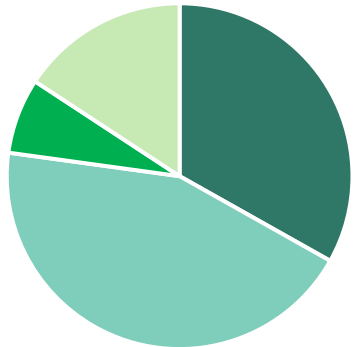
# The Promise of Natural Products



ca. 55%  
All small molecule drugs

Small Molecule Anticancer drugs, 1981-2020

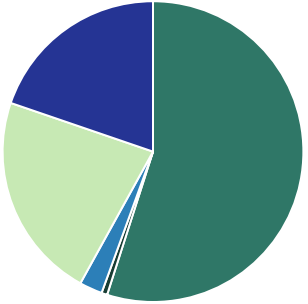
>80%



- Natural Products
- Natural Product Mimics
- Synthetic with NP pharmacophore
- Synthetic

Antibacterial drugs, 1981-2020

>60%



- Natural Products
- Synthetic with NP pharmacophore
- Biological Macromolecule
- Synthetic
- Vaccines

Journal of Natural Products (2016) 79(3)





# Ethnobotany Discovery

> 28,000 plant species in use as medicine in 90 countries  
<10% have been checked for active molecules



*Peniocereus greggii*



*Cirsium ochrocentrum*



*Aralia nudicaluis*



*Arbutus menziesii*



*Lewisia rediviva*



*Anenopsis californica*



*Opuntia spp.*

Frontiers in pharmacology 4 (2014): 177  
<https://phys.org/news/2017-05-uk-survey-species-medical.html> (2017)





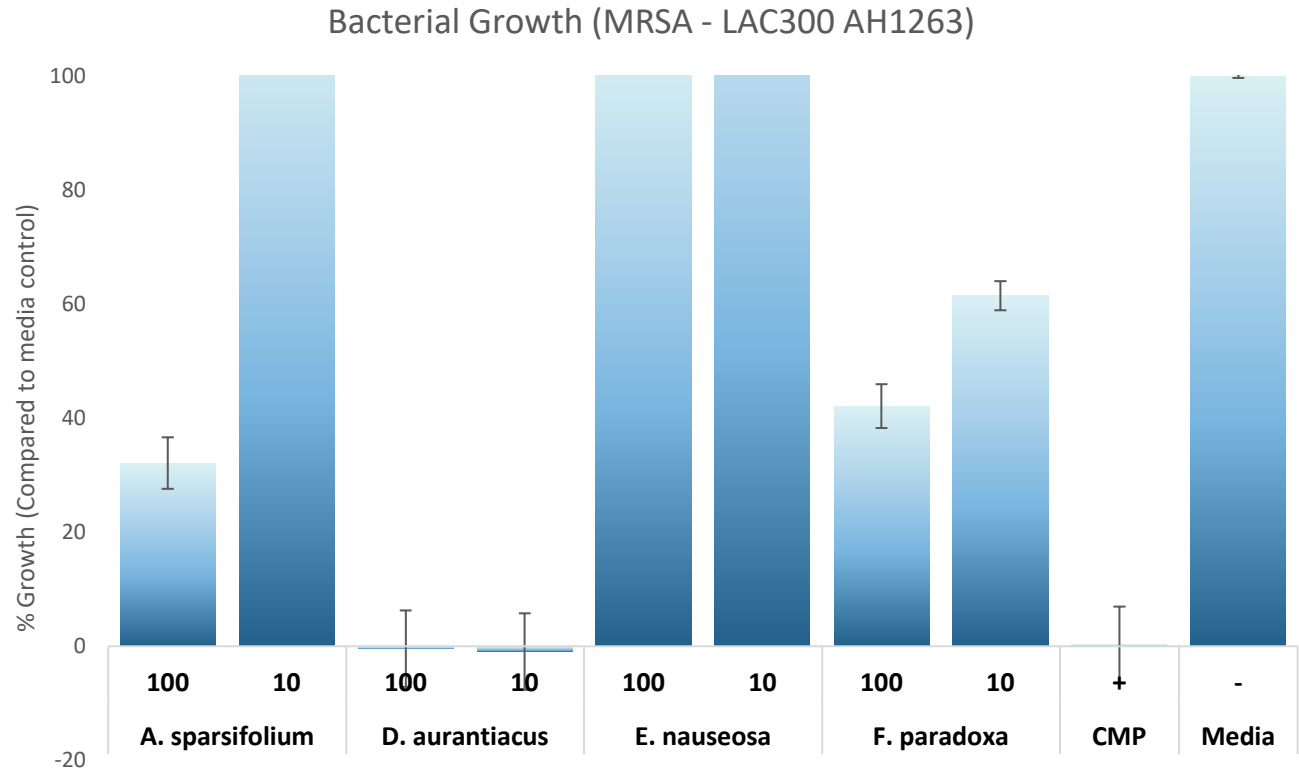
# NA Ethnobotanical Leads



*Adenostoma sparsifolium*  
"Red shanks"



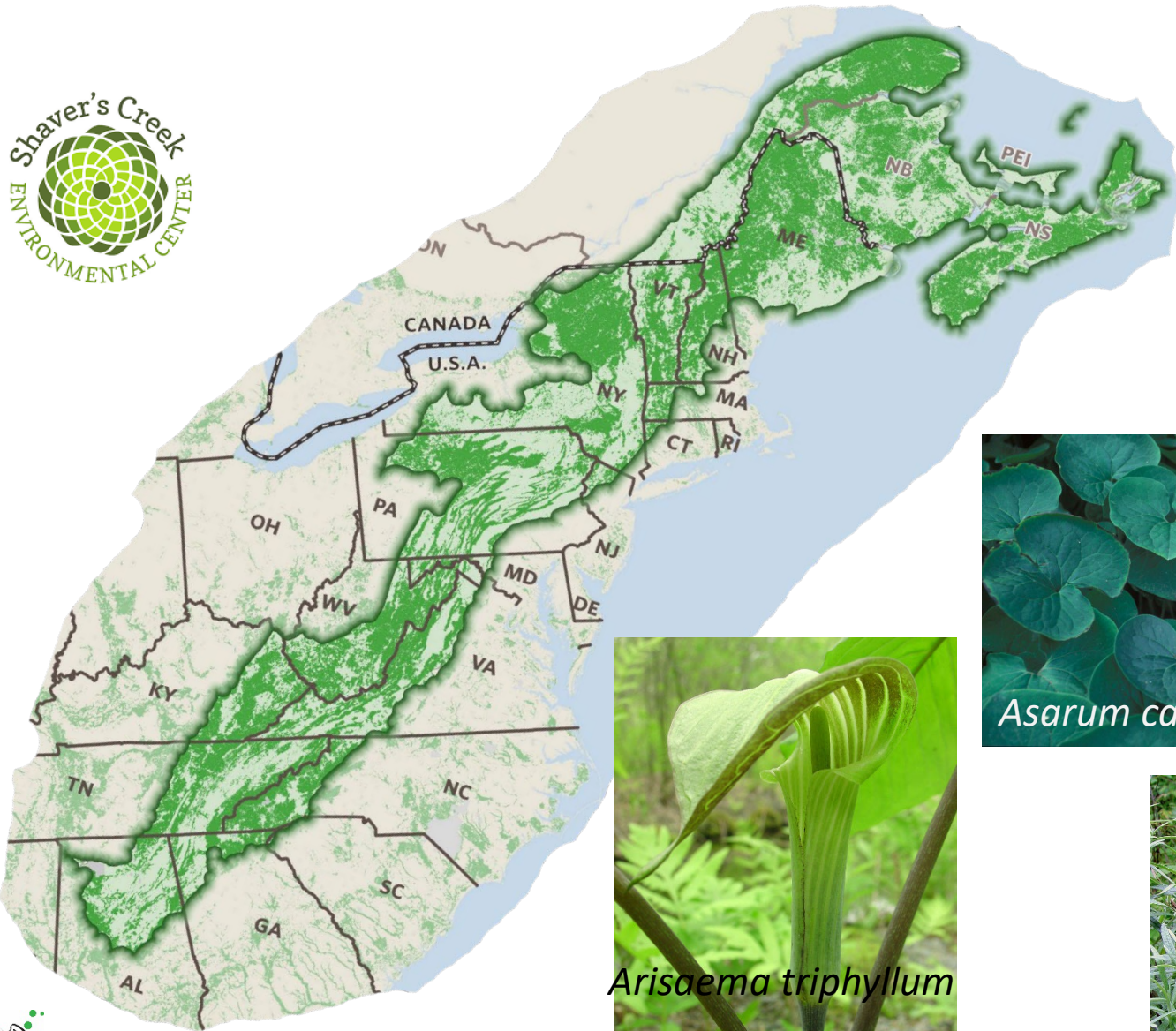
*Fallugia paradoxa*  
"Apache plume"  
*Diplicaucus aurantiacus*  
"Monkey flower"



*Ericameria nauseosa*  
"Rubber rabbitbrush"



# Appalachian Plants



*Pilea pumila*



*Asarum canadense*



*Gnaphalium uliginosum*



*Arisaema triphyllum*



*Anaphalis margaritacea*





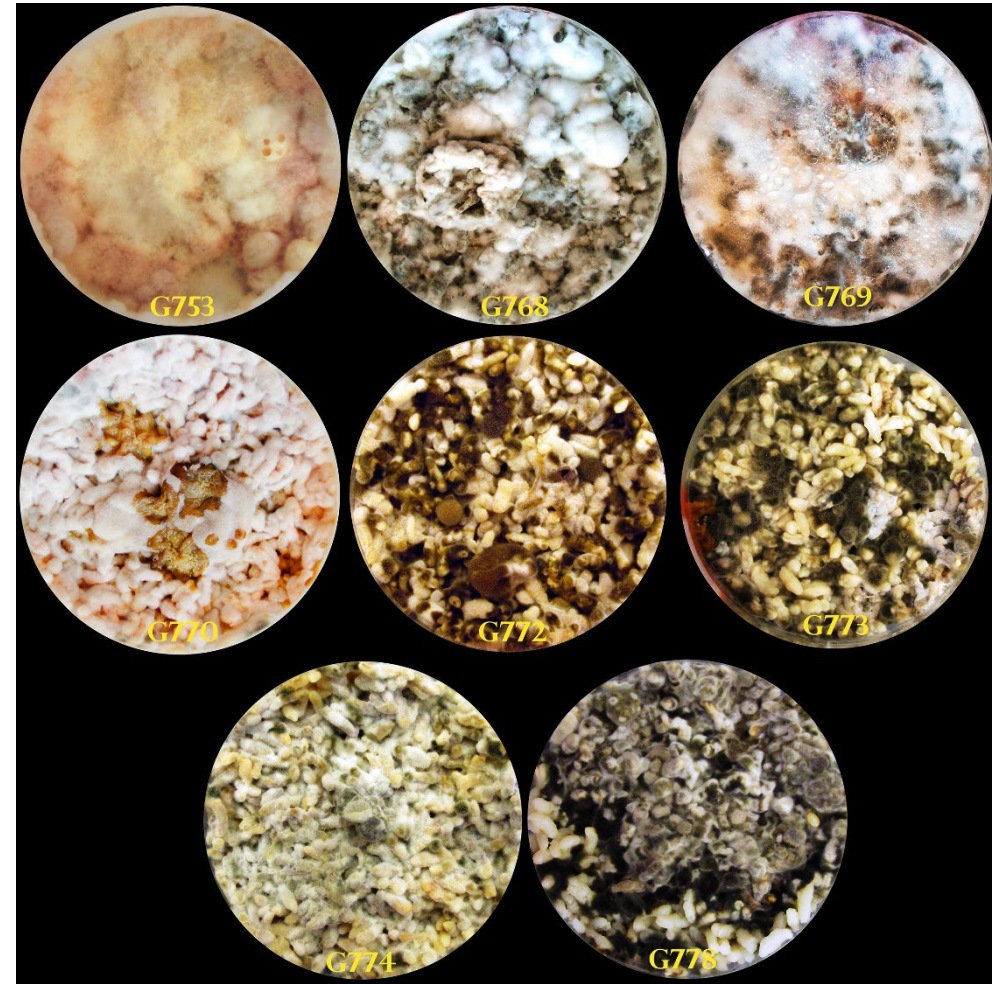
# Ethnobotanical Collaborations





# Microbial Natural Products

## Fungi, Lichens, & Endosymbiotic Organisms



## Urban park soil microbiomes are a rich reservoir of natural product biosynthetic diversity

Zachary Charlop-Powers<sup>a</sup>, Clara C. Pregitzer<sup>b</sup>, Christophe Lemetre<sup>a</sup>, Melinda A. Ternei<sup>a</sup>, Jeffrey Maniko<sup>a</sup>, Bradley M. Hover<sup>a</sup>, Paula Y. Calle<sup>a</sup>, Krista L. McGuire<sup>c,d</sup>, Jeanne Garbarino<sup>e</sup>, Helen M. Forgione<sup>b</sup>, Sarah Charlop-Powers<sup>b</sup>, and Sean F. Brady<sup>a,1</sup>

AMERICAN SOCIETY FOR MICROBIOLOGY Applied and Environmental Microbiology®

MICROBIAL ECOLOGY



Volume 165, Issue 11

Research Article | Open Access

### Awakening ancient polar *Actinobacteria*: diversity, evolution and specialized metabolite potential

Natalie Millán-Aguiñaga<sup>1</sup>, Sylvia Soldatou<sup>2</sup>, Sarah Brozio<sup>2</sup>, John T. Munnoch<sup>2</sup>, John Howe<sup>3</sup>, Paul A. Katherine R. Duncan<sup>2</sup>

View Affiliations

Published: 01 November 2019 | <https://doi.org/10.1099/mic.0.000845>

Info Sections

Side by side view PDF Tools



## Detection of Natural Products and Their Producers in Ocean Sediments

Robert N. Tuttle,<sup>a</sup> Alyssa M. Demko,<sup>a</sup> Nastassia V. Patin,<sup>a\*</sup> Clifford A. Kapon,<sup>b</sup> Mohamed S. Donia,<sup>c</sup> Pieter Dorrestein,<sup>b,d</sup> Paul R. Jensen<sup>a,d</sup>

ASM Journals / Applied and Environmental Microbiology / Vol. 78, No. 10 / Natural Product Biosynthetic Gene Diversity in Geographically Distinct Soil Microbiomes

Research Article | 24 April 2012

## Natural Product Biosynthetic Gene Diversity in Geographically Distinct Soil Microbiomes

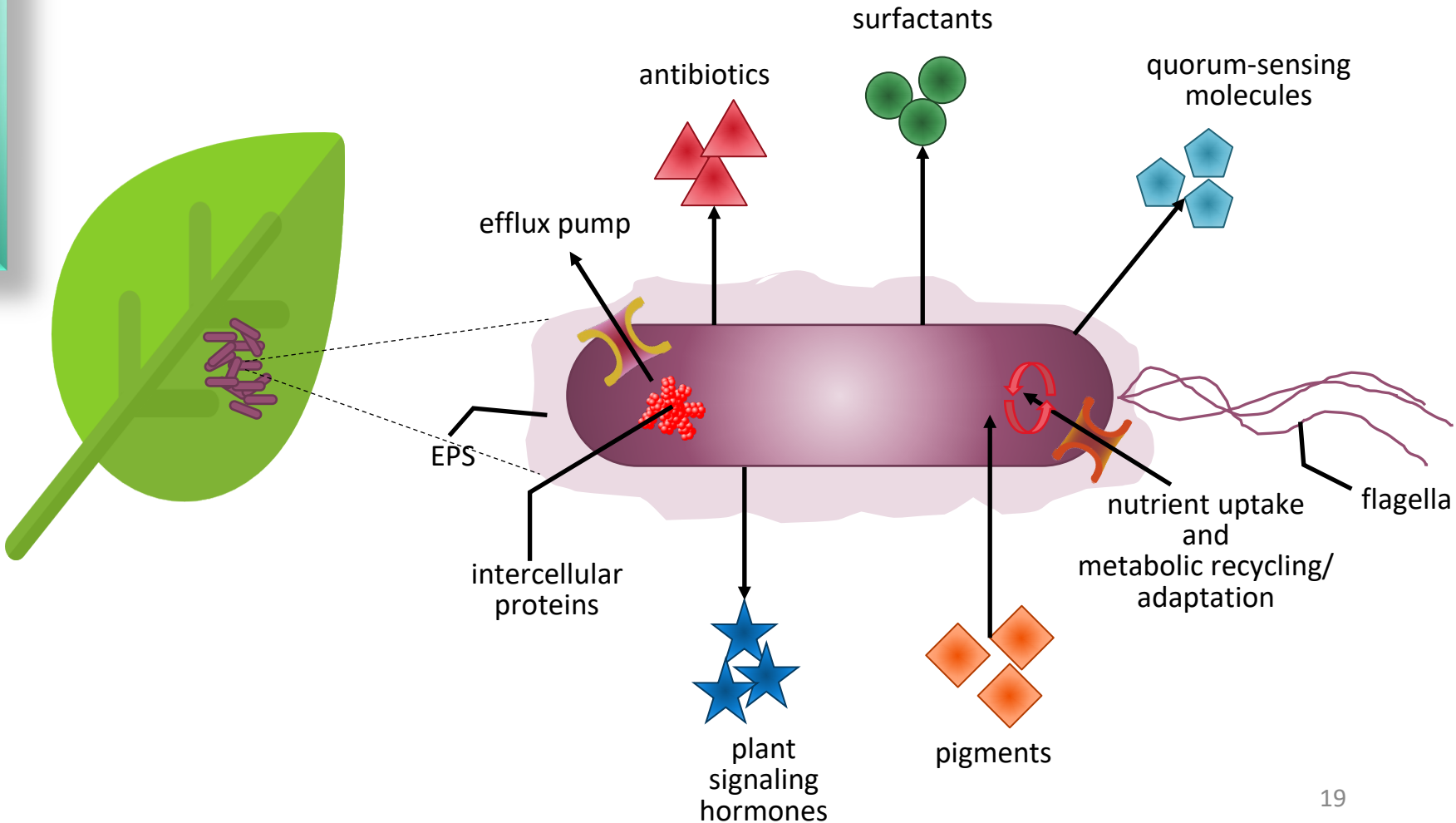
Authors: Boojala Vijay B. Reddy, Dimitris Kallifidas, Jeffrey H. Kim, Zachary Charlop-Powers, Zhiyang Feng, Sean F. Brady | [AUTHORS INFO & AFFILIATIONS](#)

DOI: <https://doi.org/10.1128/AEM.00102-12> Check for updates

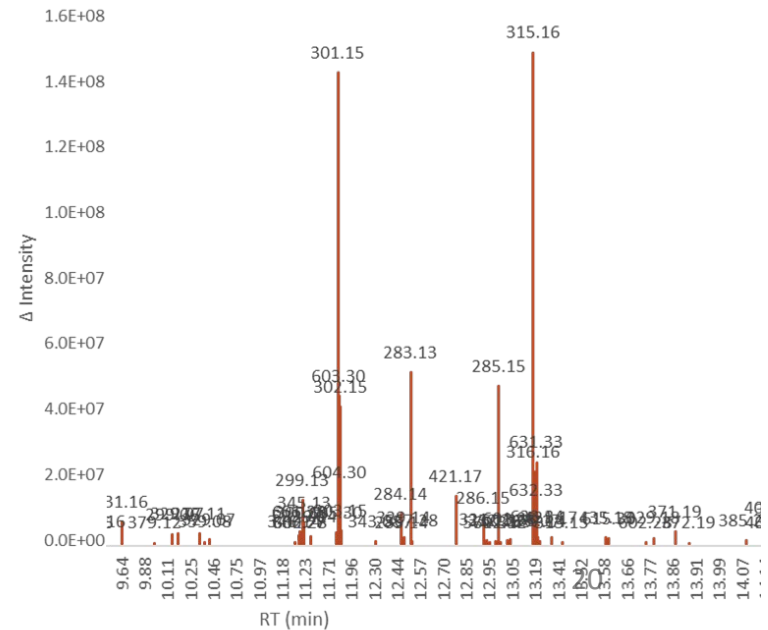
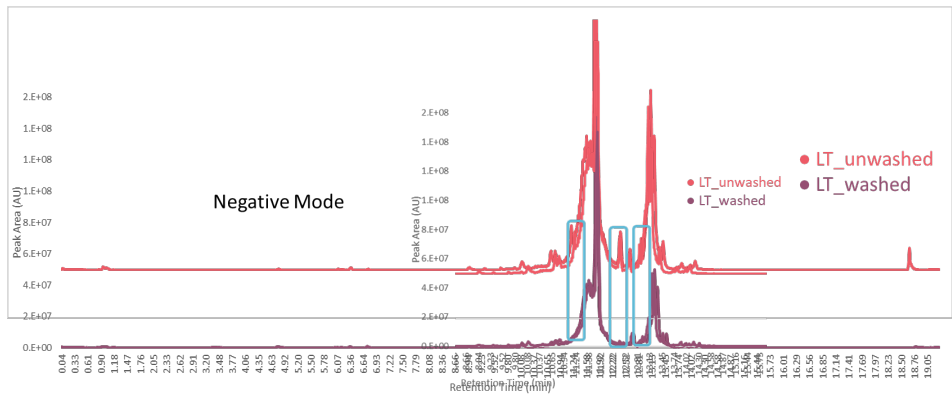
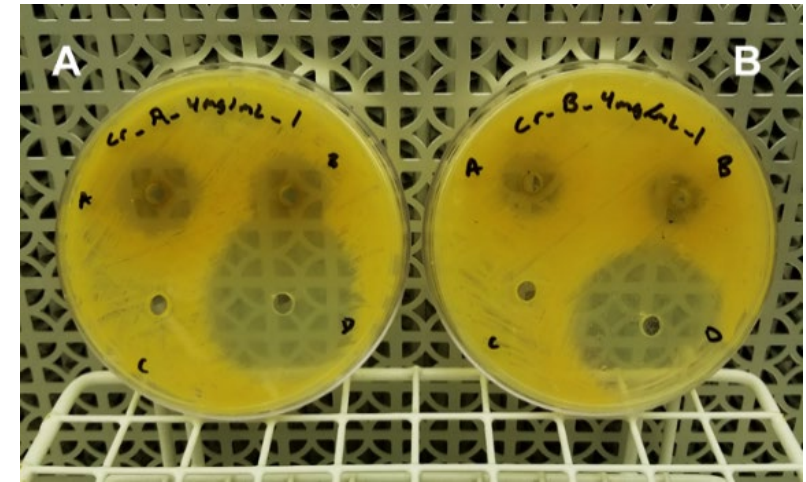
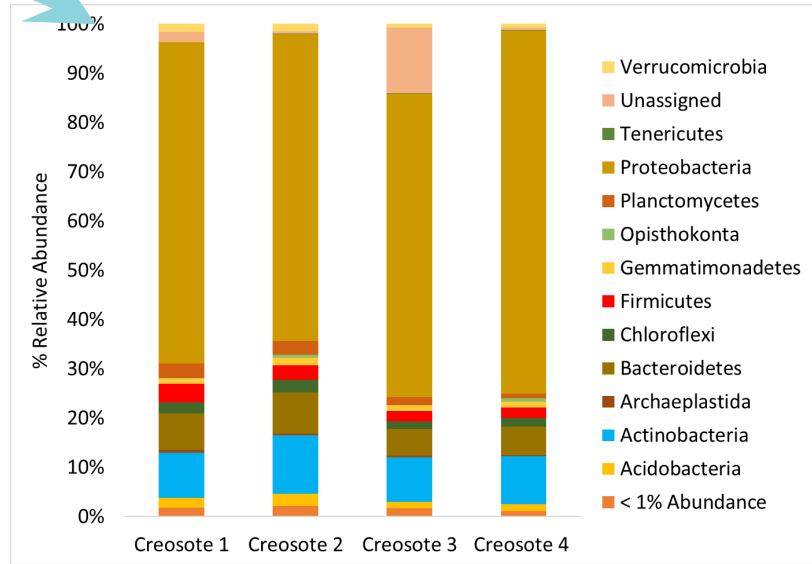


# A Hostile Environment, An Opportunity for Adaptation

- limited nutrient availability
- exposure to ultraviolet radiation
- oxidative stress
- drought
- rapidly-changing abiotic conditions.

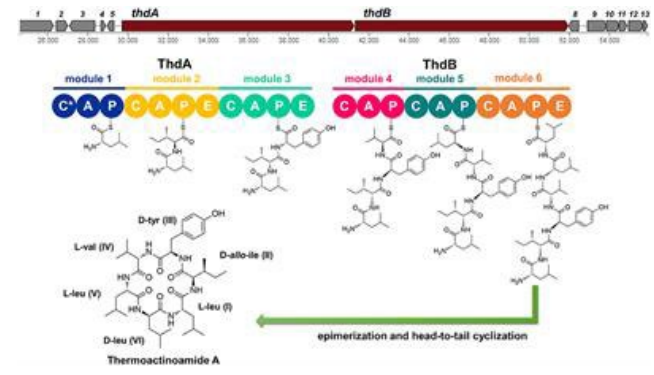
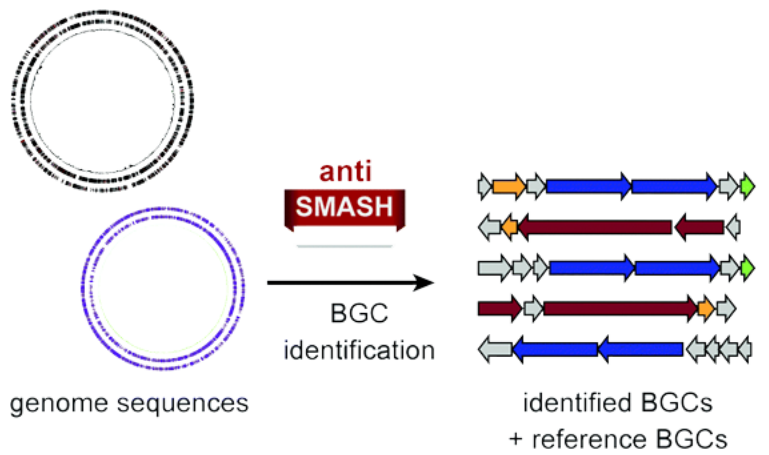
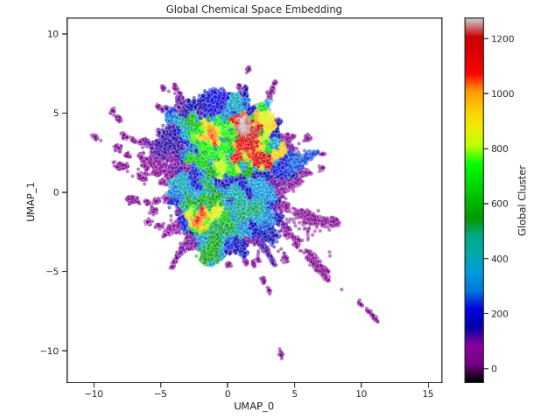
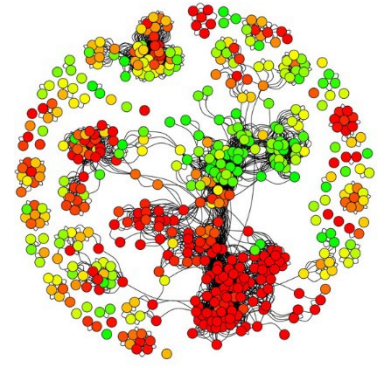
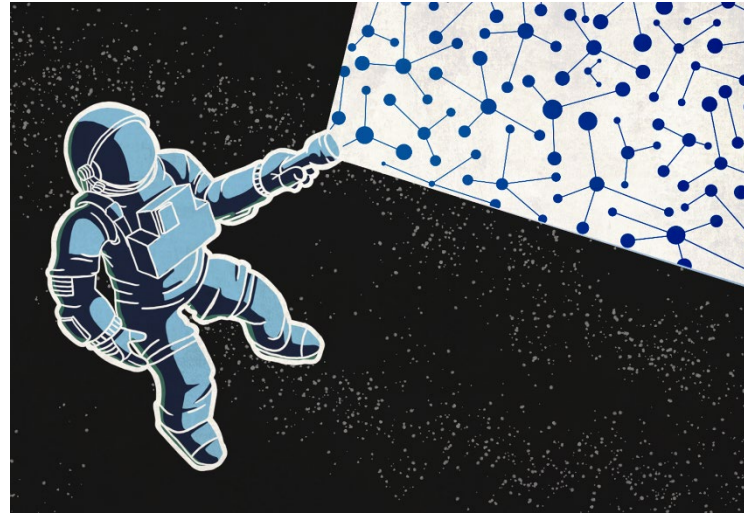


# Antibacterial phyllosphere from *Larrea tridentata*





# Exploring Environmental Microbiomes at SURF

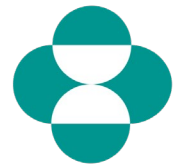




# Acknowledgements



National Institute of Allergy and Infectious Diseases



**MERCK**



American Society of Pharmacognosy



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College of Agricultural Sciences



**PennState**  
Huck Institutes of the Life Sciences





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[www.sites.psu.edu/kellogglab](http://www.sites.psu.edu/kellogglab)

@jk Kellogg916



Thank you!  
Questions?