Stilbene a new antibiotic class for topical and systemic administration

Jason M. Crawford, Ph.D.

(Hyun Bong Park, Ph.D., Tyler Goddard)

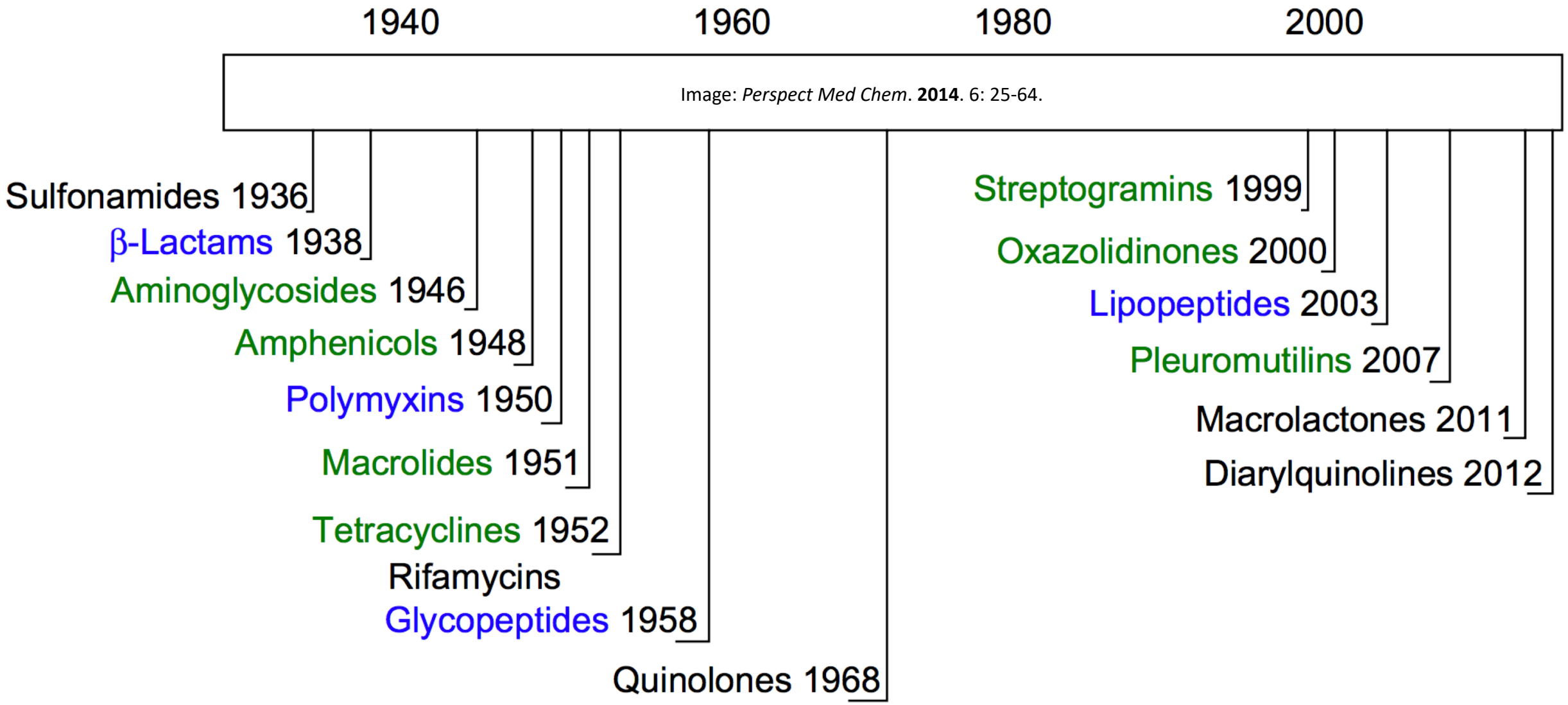
crawfordlab.yale.edu

Mucosinix Pharm

This is a Unique and Critical Time for Antibiotic Drug Development

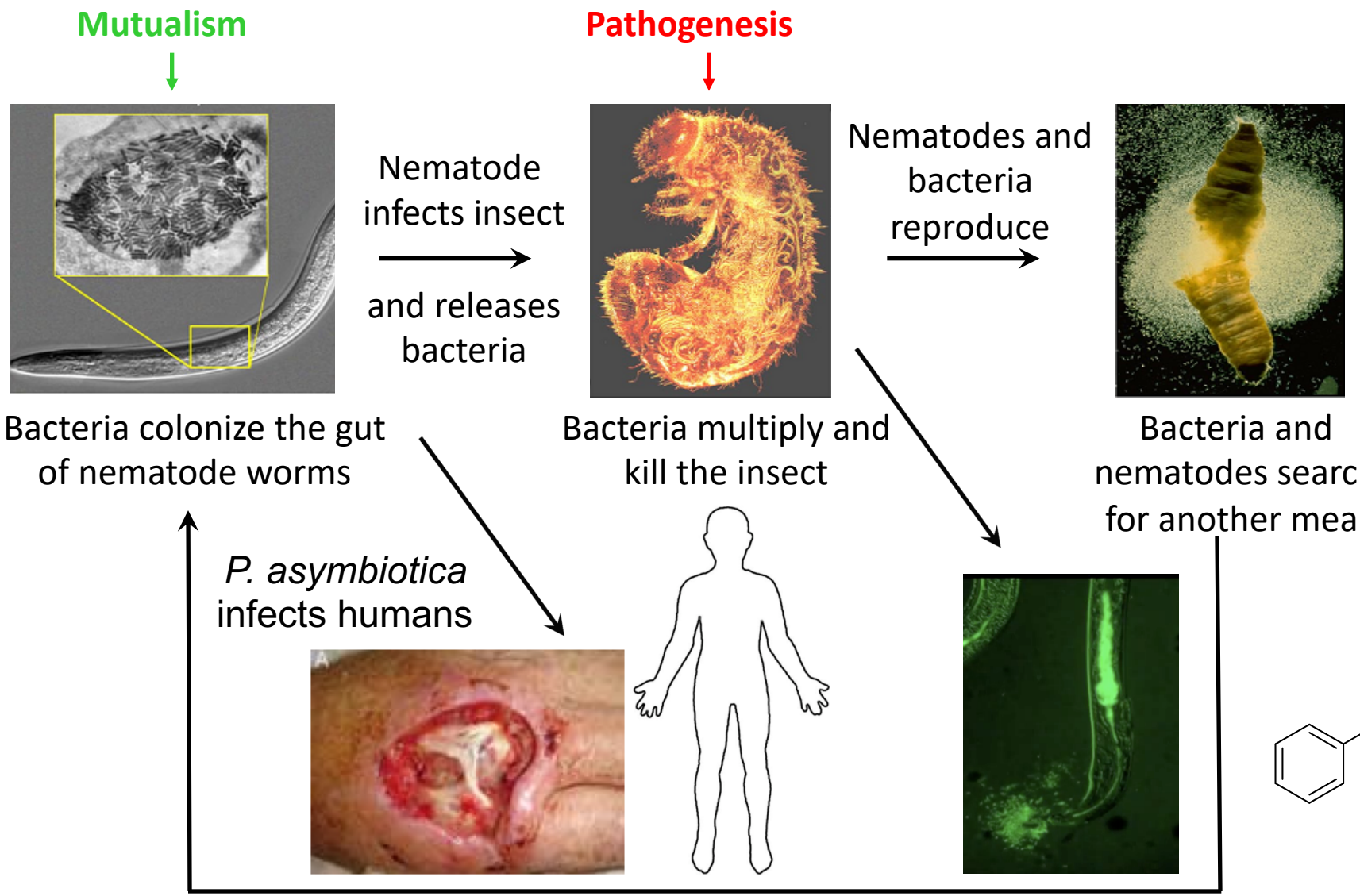
- **Overcrowding and overburdening of hospitals due to the COVID-19 pandemic**
  - **Reuse of PPE and sharing of ventilators due to limited resources**
  - **Poorer compliance for reporting antibiotic use and infection rates**
  - **Anecdotal surging antibiotic use to treat COVID-19**
- **Result is a climate encouraging the spread of multi-drug resistant organisms**
- **Viral illnesses increase susceptibility for secondary bacterial infections (secondary bacterial pneumonia has historically been a notable cause of death during viral pandemics)**
- **DISARM Act of 2019 introduced to the House (Subcommittee on Health)**
  - **Proposes increasing hospital reimbursement for antibiotics, and incentivizing development of robust effective antimicrobial stewardship programs**
- **NOW IS THE TIME TO ACT!**

Antibiotic classes are limited and drug resistance is climbing



- **Antibiotic resistance is a major health crisis**
- **ribosome inhibitors; cell wall inhibitors**

Photorhabdus EVOLVED antimicrobials to protect their food source

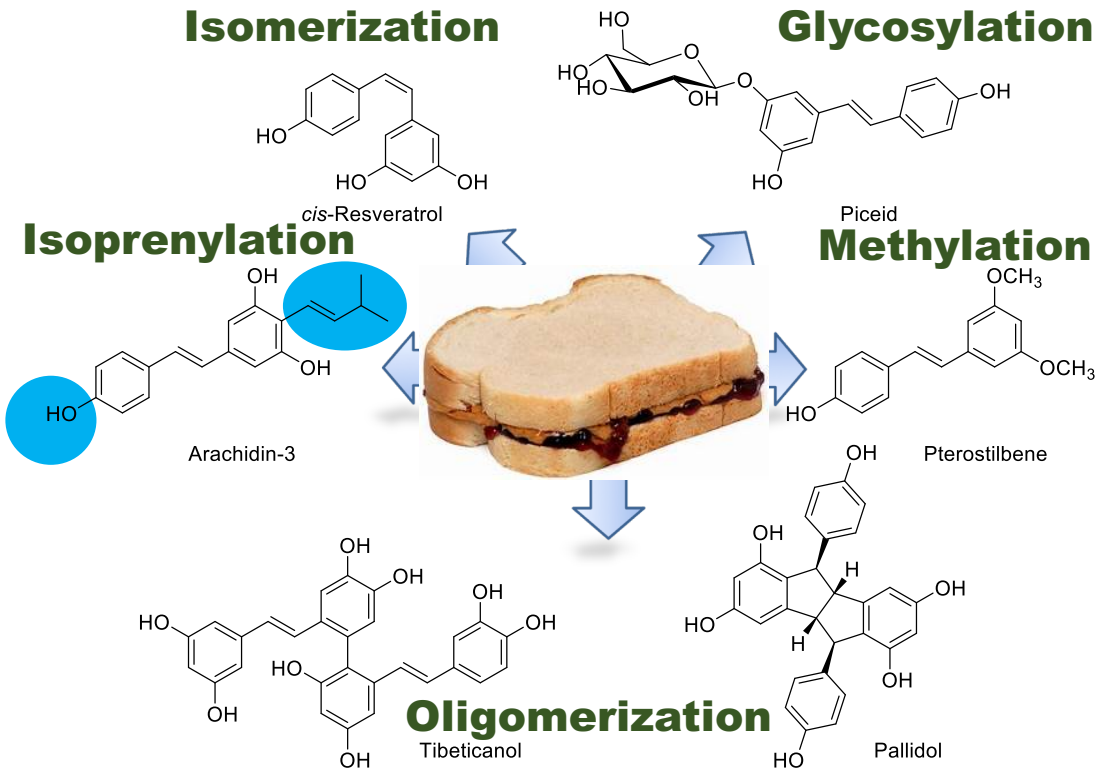


Somvanshi, V.S. et al. *Science* **2012**, *337*, 88-93.

Waterfield, N. **2009**. *Annu. Rev. Micro*. 63: 557.

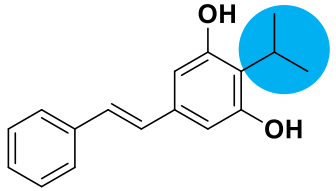
Stilbenes are polyketides widely distributed in dietary plants

Plant Stilbene Diversification



- Stilbene supplements can alleviate IBD symptoms

Bacterial stilbene (substrate)



- **Tapinarof**

ANTIBIOTICS IN MICROBIAL ECOLOGY
Isolation and Structure Assignment of Several New Antibacterial Compounds from the Insect-Symbiotic Bacteria *Xenorhabdus* spp.

VALERIE J. PAUL, SALLY FRAUTSCHY, WILLIAM FENICAL, and KENNETH H. NEALSON

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Dec. 1995, p. 4329–4333 Vol. 61, No. 12
0099-2240/95/$04.00+0
Copyright © 1995, American Society for Microbiology

Identification of Two Pigments and a Hydroxystilbene Antibiotic from *Photorhabdus luminescens*

JIANXIONG LI,[1]* GENHUI CHEN,[1] HOUMING WU,[2] AND JOHN M. WEBSTER[1]

Department of Biological Sciences, Simon Fraser University, Burnaby, Vancouver, British Columbia V5A 1S6, Canada,[1] and State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China[2]

Received 27 July 1995/Accepted 15 August 1995

PNAS

An antibiotic produced by an insect-pathogenic bacterium suppresses host defenses through phenoloxidase inhibition

Ioannis Eleftherianos*, Sam Boundy*, Susan A. Joyce*, Shazia Aslam*, James W. Marshall†, Russell J. Cox‡, Thomas J. Simpson‡, David J. Clarke*, Richard H. ffrench-Constant‡, and Stuart E. Reynolds*§

*Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, United Kingdom; †School of Chemistry, University of Bristol, United Kingdom; and ‡Centre for Ecology and Conservation, University of Exeter, Cornwall Campus, Penryn TR10 9EZ, United Kingdom

Communications

VIP Biosynthesis

Bacterial Biosynthesis of a Multipotent Stilbene**

Susan A. Joyce, Alexander O. Brachmann, Itamar Glazer, Lea Lango, David J. Clarke, and Helge B. Bode**

ORIGINAL ARTICLE

Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis: results from a randomized double-blind placebo-controlled, phase II trial

R. Bissonnette,†,* C. Bolduc,† C. Maari,† S. Nigen,† J.M. Webster,‡ L. Tang,‡ M. Lyle‡

†Innovaderm Research Inc., Montreal, QC, Canada
‡Department of Research and Development, Welichem Biotech Inc., Burnaby, BC, Canada
*Correspondence: R. Bissonnette. E-mail: rbissonnette@innovaderm.ca

CHEMMEDCHEM COMMUNICATIONS

ChemPubSoc Europe

DOI: 10.1002/cmdc.201300057

From a Multipotent Stilbene to Soluble Epoxide Hydrolase Inhibitors with Antiproliferative Properties

Estel.la Buscató,[a] Dominik Büttner,[a] Astrid Brüggerhoff,[a] Franca-Maria Klingler,[a] Julia Weber,[a] Bastian Scholz,[b] Aleksandra Živković,[a] Rolf Marschalek,[b] Holger Stark,[a] Dieter Steinhilber,[a] Helge B. Bode,[c] and Ewgenij Proschak*[a]

ORIGINAL ARTICLE

See related commentary on pg 2050

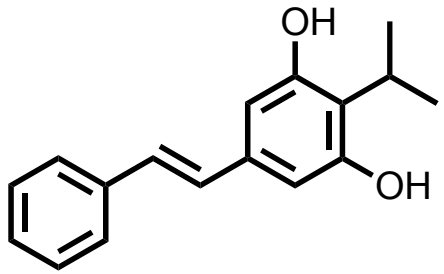
Tapinarof Is a Natural AhR Agonist that Resolves Skin Inflammation in Mice and Humans

Susan H. Smith[1,7,*], Channa Jayawickreme[2,7,*], David J. Rickard[2,*], Edwige Nicodeme[3,*], Thi Bui[1,*], Cathy Simmons[2,*], Christine M. Coquery[1,*], Jessica Neil[1,*], William M. Pryor[1,*], David Mayhew[3,*], Deepak K. Rajpal[2,*], Katrina Creech[2,*], Sylvia Furst[2,*], James Lee[1,*], Dalei Wu[2,*], Fraydoon Rastinejad[2,*], Timothy M. Willson[2,*], Fabrice Viviani[2,*], David C. Morris[1,*], John T. Moore[2,*] and Javier Cote-Sierra[1,*]

- Clinical efficacy for psoriasis & atopic dermatitis (GSK)
- Activates AhR (nm) and Nrf2 to promote clinical efficacy

Duotap: A Novel Antibiotic with a New Indication

- **Antibiotic market for MRSA antibiotics (1.3 billion market by 2026)**



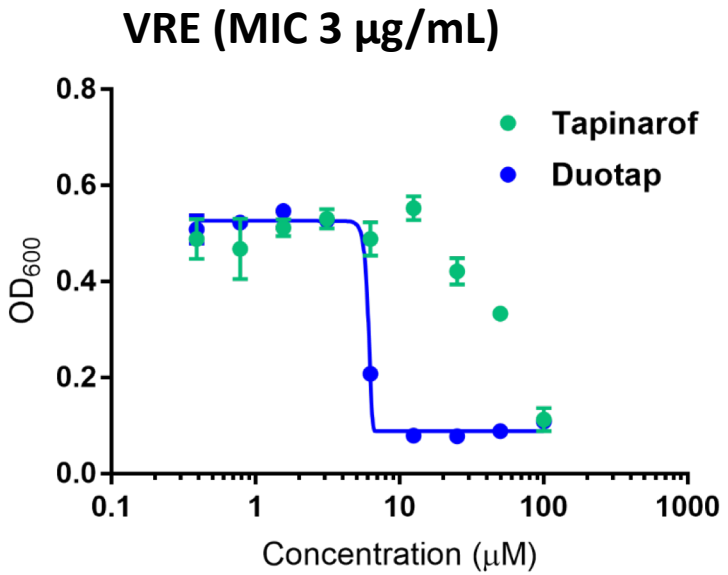
GSK recently sold **Tapinarof** to Dermavant Sciences for **$330 million**

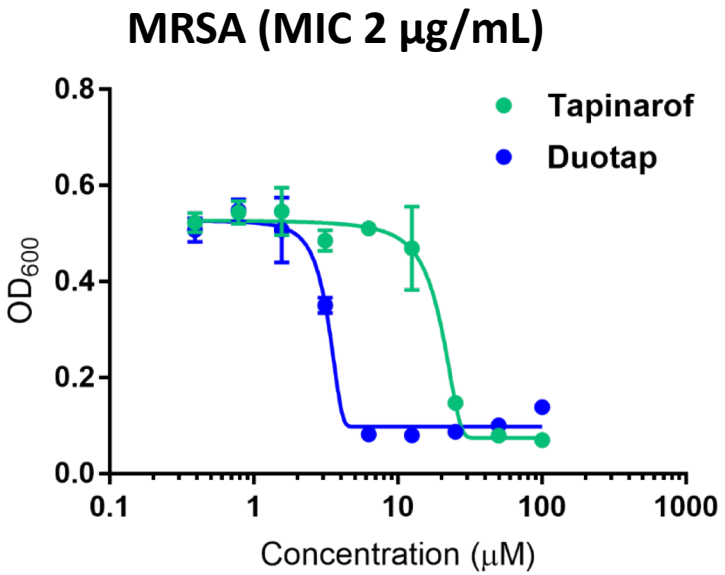
MUX-001 Drug Lead ("Duotap")

Using evolution as a guide, we discovered **MUX-001**, a **novel stilbene** drug lead for **MRSA**

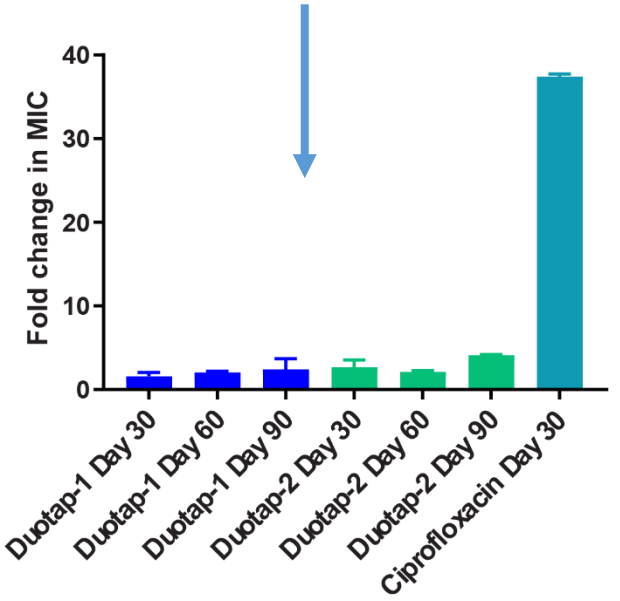
Duotap is effective against drug resistant bacteria

MUX-001
Drug Lead
(Duotap)



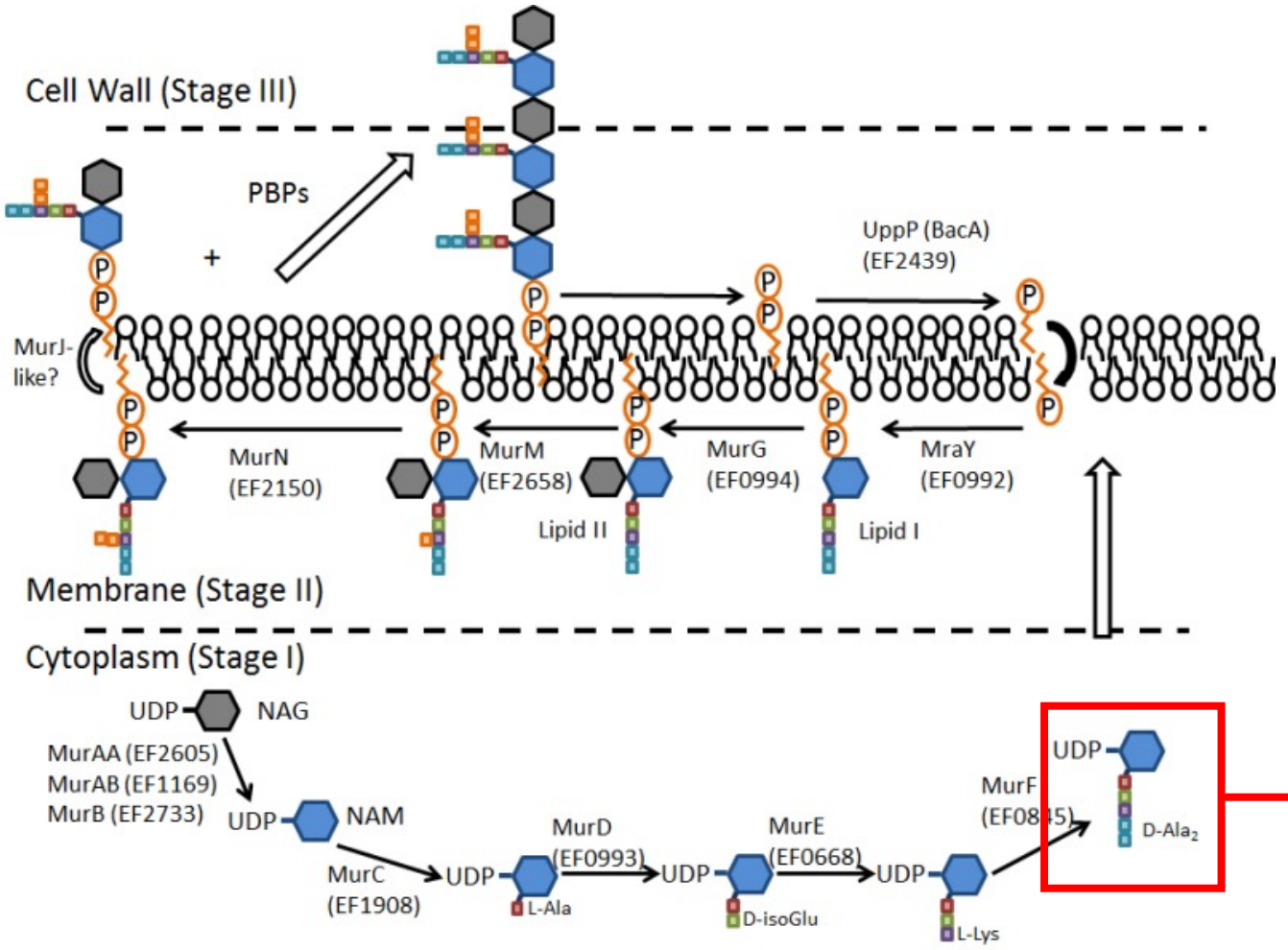


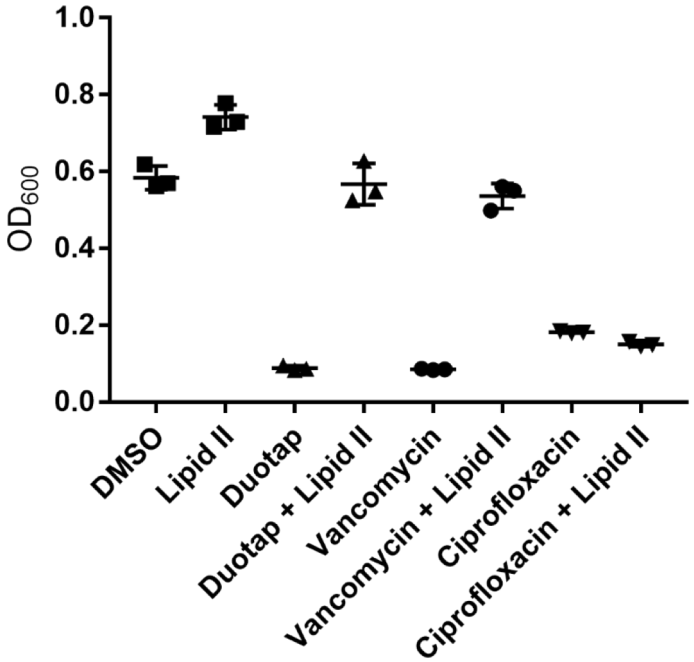
- **New class effective against multidrug resistant organisms (Cell wall biosynthesis inhibitor)**
- **MRSA does not develop resistance to MUX-001**

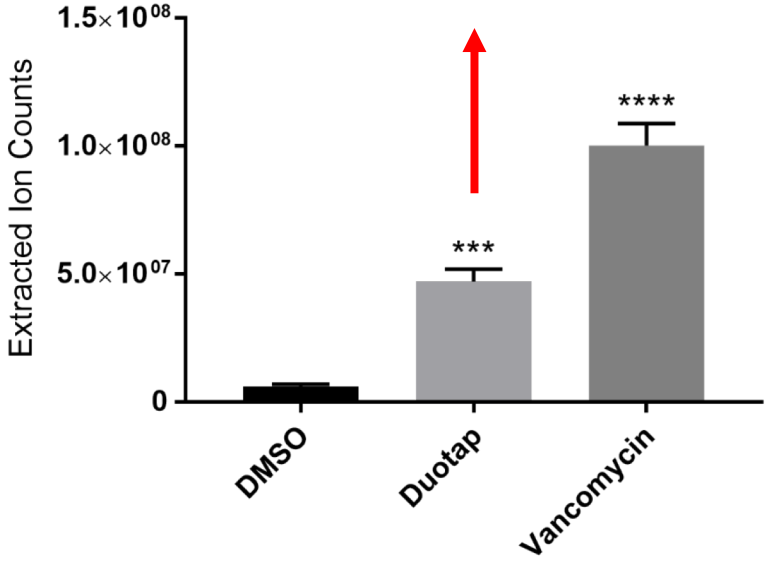


Tyler Goddard & Hyun Bong Park

Duotap inhibits cell wall biosynthesis







Tyler Goddard & Hyun Bong Park

Image: Hancock, L.E., Murray, B.E., Sillanpaa, J. *Enterococcal Cell Wall Components and Structures.*

Funded Animal Study

- **Efficacy Assessment in Murine MRSA Dermal Infection Model**
- **Contracted through TransPharm Preclinical Solutions**
- **Funding already secured through YCCI Research Support Award**
  - **Female, SKH-1 hairless mice ordered from Charles River**
  - **Targeted challenge inoculate of 6.0 log10 CFU organisms per 100 µL Methicillin resistant Staphylococcus aureus**
  - **Test articles will be administered topically at 4, 8 and 12 hours**
  - **Efficacy of test articles will be determined by comparison of CFU per gram of tissue between the vehicle group and test article groups**
- **Results in progress**

IP/ Budget

IP: Provisional patent filed for compositions of matter and methods of use.

- **Biocatalytic pipeline to generate Mux analogs (new compositions of matter)**
- **Use as an anti-infective against MDR pathogens (provisional in place)**

2-year proposal: $100K (Phase 1)

- **Phase 1**

Topical dose ranging study	**$30,000**
Oral and intraperitoneal PK study	**$30,000**
Pan laboratories liver microsome study and P450 preliminary tox study	**$40,000**

- **Phase 2**

Medicinal chemistry program with Jubilant for oral bioavailability	**$200,000**