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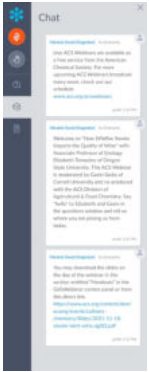
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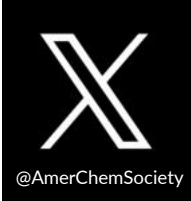


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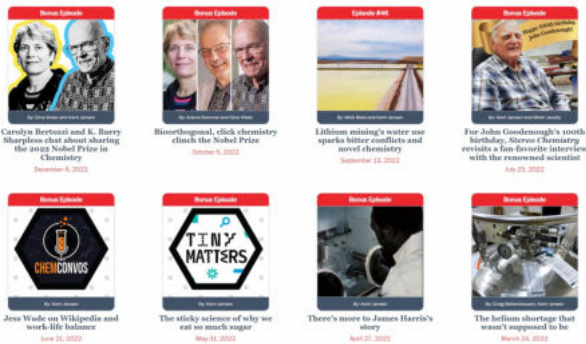
Sam Jones, PhD
Science Writer & Exec Producer

Deboki Chakravarti, PhD
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 December 6, 2022

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 October 6, 2022

Episode #3
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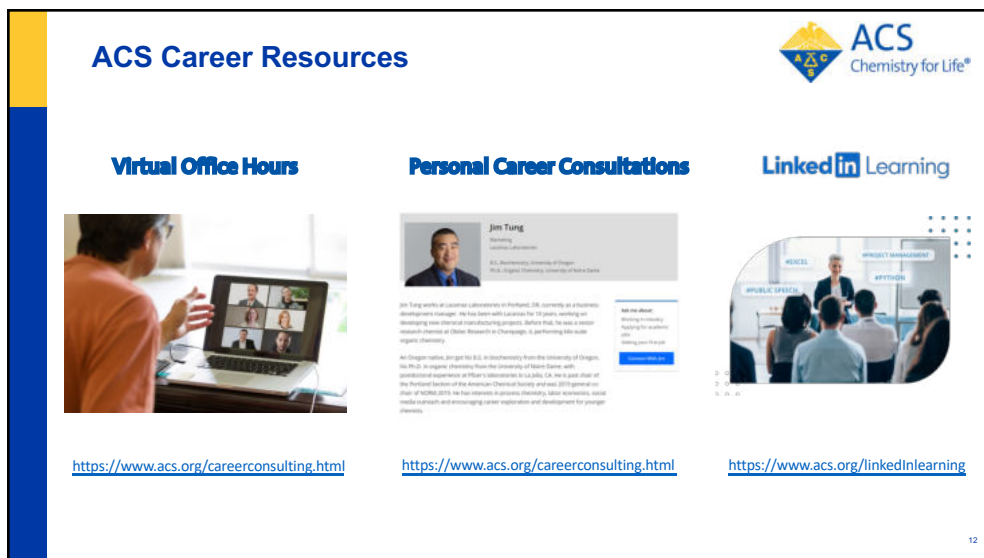
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Personal Career Consultations

Jim Tung
 Director
 ACS, Department of Chemistry, University of Oregon


Jim Tung serves as a career advisor on LinkedIn, currently as an academic development manager. He has been with LinkedIn for 12 years, working on developing new content and manufacturing partners. Before that, he was a senior research scientist at Oracle Research in Chicago, leading the mobile organic chemistry.

At Oregon State, Jim got his B.S. in biochemistry from the University of Oregon. He then did a master's thesis from the University of Texas at Austin, with postdoctoral experience at Pfizer's laboratories in La Jolla, CA. He is past chair of the Portland Section of the American Chemical Society and was 2015 general chair of ACSOR 2015. He has interests in process chemistry, labor economics, social media networks and encouraging career exploration and development for younger chemists.

[Ask Jim about:](#)
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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

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Diversity, Equity, Inclusion, and Respect

Equity**
Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**
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Inclusion**
Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect
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****Adapted from definitions from the Ford Foundation Center for Social Justice.**

<https://www.acs.org/diversity>

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American Chemical Society <https://www.acs.org/policy> 15

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Cutting Edge Antibiotic and Gene Therapy Research



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Distinguished Professor, New Chemistry Unit
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Nehru Centre for Advanced Research



KARMELLA A. HAYNES, PHD
Associate Editor, ACS Synthetic Biology
and Assistant Professor, Wallace H.
Coulter Department of Biomedical
Engineering, Emory University



CATHERINE GOODMAN, PHD
Senior Associate Publisher,
American Chemical Society

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**Pursuit of Next-Generation Glycopeptides:
A Journey with Vancomycin**

Jayanta Haldar
Professor
Editor-in-Chief of *ACS Infectious Diseases*
Antimicrobial Research Laboratory
New Chemistry Unit (NCU) and
School of Advanced Materials (SAMAT)
Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR)
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Email: jayanta@incasr.ac.in Twitter: @jayanta_amr
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ACS Infectious Diseases

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Plan of the Talk

- ❖ Glycopeptide antibiotics (Vancomycin) and mechanisms of action
- ❖ Inherent and acquired resistance to glycopeptides
- ❖ Next-generation glycopeptides to tackle resistance and complicated infections

2

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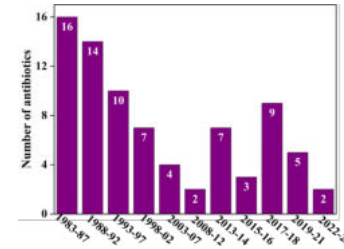
Antimicrobial Resistance (AMR) – Global Threat

Impact of AMR

- ❖ 700,000 deaths annually
- ❖ 10 million deaths annually by 2050
- ❖ \$100 trillion by 2050



Number of antibiotics approved

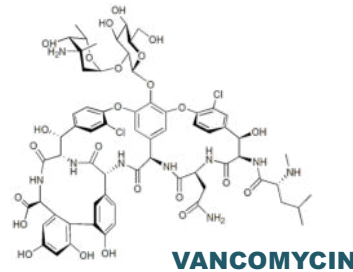


- Gap between the availability of new antibiotics and increasing severity of AMR is threatening to push the world towards a pre-antibiotic era.

Haldar & coworkers *J. Med. Chem.* 2019, 62, 3184
Blair et al. *Nat. Rev. Microbiol.* 2015, 13, 42
www.paho.org, www.cdc.gov
<https://amr-review.org/>

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Vancomycin: A natural glycopeptide antibiotic



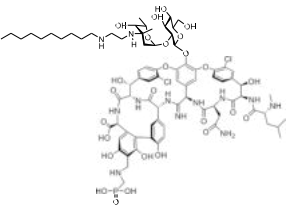
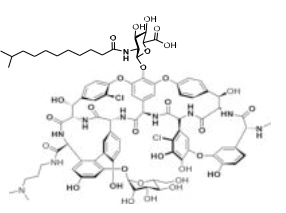
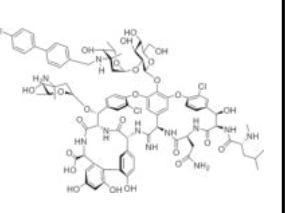
- ❖ **Isolated:** from soil bacterium *Amycolatopsis orientalis* in 1952
- ❖ **Approved:** FDA 1958

TEICOPLANIN

- ❖ **DRUG OF LAST RESORT**
- ❖ Used to treat: **Gram-positive** lethal bacterial infections such as Staphylococcal (MRSA), Enterococcal, *Clostridium difficile* infections
- ❖ **Diseases:** sepsis, endocarditis, skin infections, bone infection, pneumonia, *Clostridium difficile*-associated diarrhea etc.
- ❖ Side effects: kidney damage and hearing loss

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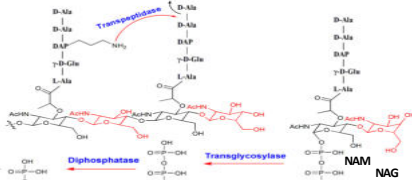
Clinically approved Semi-synthetic glycopeptides

TELAVANCIN	DALBAVANCIN	ORITAVANCIN
		
Approved in 2009	Approved in 2014	Approved in 2014
<ul style="list-style-type: none"> Complicated skin and skin-structure infections (cSSSI) Hospital-acquired and ventilator-associated pneumonia caused by <i>S. aureus</i>, enterococci & streptococci. 	<ul style="list-style-type: none"> Acute skin and skin-structure infections caused by methicillin-susceptible and resistant <i>S. aureus</i> (MSSA, MRSA), Streptococci and vancomycin sensitive <i>E. faecalis</i> 	<ul style="list-style-type: none"> Acute skin and tissue infections caused by MRSA, MSSA, Streptococci and vancomycin-susceptible <i>E. faecalis</i>

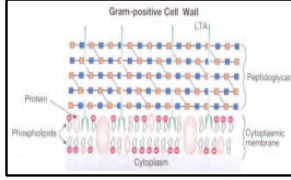
Paramita Sarkar *et al.*, *Med. Chem. Commun.*, 2017, 8, 516 5

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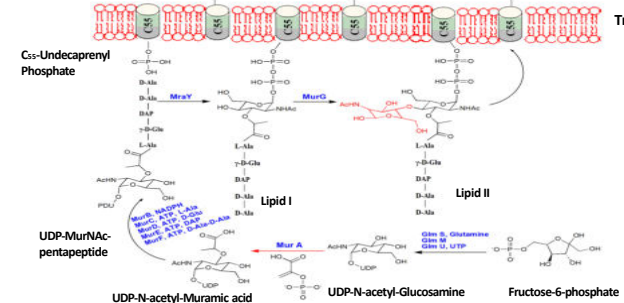
Cell Wall (Peptidoglycan) Biosynthesis


Enzymes: **Transpeptidase**, **Diphosphatase**, **Transglycosylase**



Varki A *et al.*, *Essential of Glycobiology*



Transporters/Flippases: FtsW, MurJ, AMJ

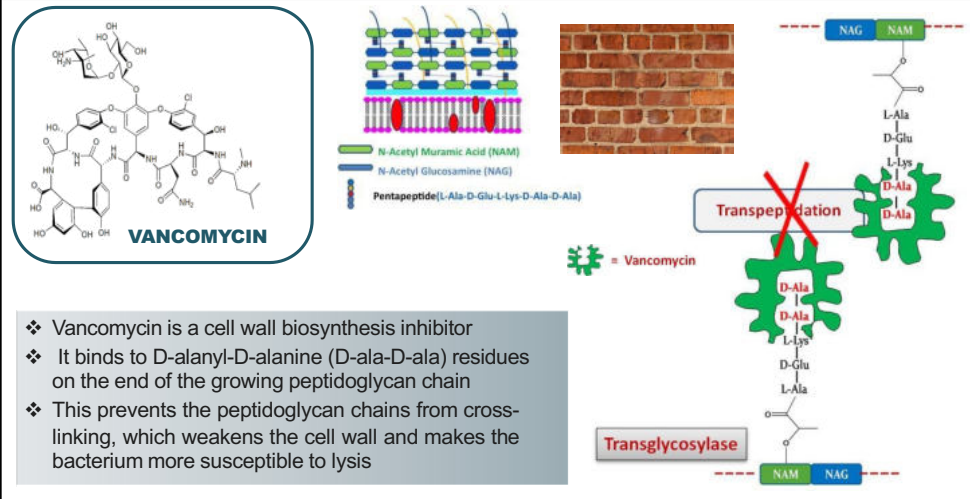


Peptidoglycan
Cytoplasmic Membrane

Paramita *et al.* *Med Chem Commun* 2017, 8, 516 6

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Vancomycin: Mechanism of action

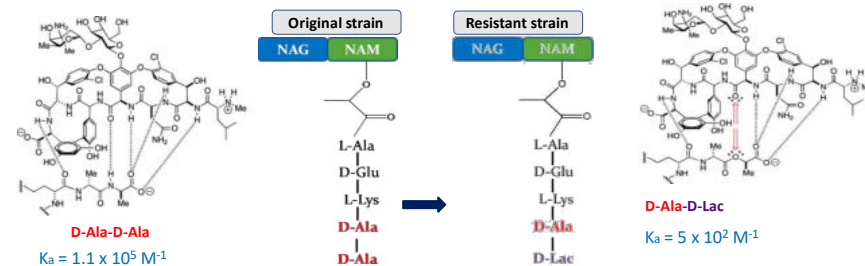


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Concern of vancomycin resistant bacteria: Acquired resistance

- ❖ Vancomycin-resistant Enterococci (VRE)
- ❖ Vancomycin-intermediate-resistant *Staphylococcus aureus* (VISA)
- ❖ Vancomycin-resistant *Staphylococcus aureus* (VRSA)

- VISA, VRSA – Thickening of cell wall
- VRE, VRSA – Target peptide changes from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser



Lack of one Hydrogen bond and the presence of lone pair repulsions:


- ❖ The binding constant decreases by $\sim 1,000$ fold
- ❖ The antibacterial activity decreases by more than 100–1,000 fold

Geetika *et al.* J Med Chem
2019, 62, 3184

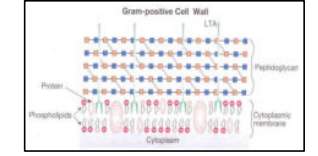
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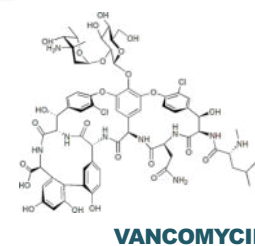
Gram-negative bacteria : Inherent resistance to vancomycin

Gram-Positive Bacteria
(Staphylococcus aureus, Enterococcus faecium)



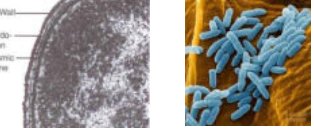
Gram-Positive Cell Wall



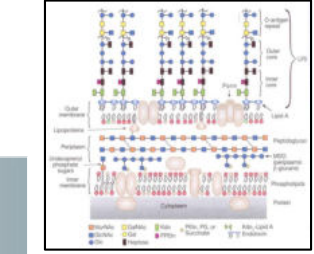


VANCOMYCIN

Gram-Negative Bacteria
(Escherichia coli, Pseudomonas aeruginosa)



Gram-Negative Cell Wall




- Vancomycin is not active against gram-negative bacteria.
- This is because gram-negative bacteria have an outer membrane (Lipopolysaccharide; LPS) that prevents vancomycin from reaching the cell wall (Periplasmic region).

Varki A et al. Essential of Glycobiology (Book) Christopher Walsh, Antibiotics: Actions, Origin, Resistance (Book) 9

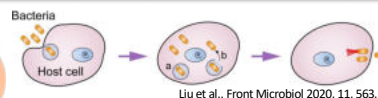
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Challenges associated with bacterial infections & Drug resistance



Varki A et al. Essential of Glycobiology

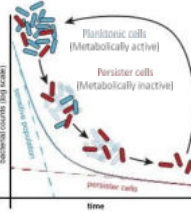
Problem-1:
Acquired resistance
(VISA, VRSA & VRE)



Liu et al., Front Microbiol 2020, 11, 563.

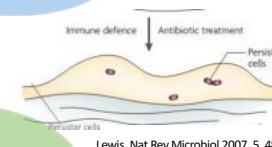
Problem-2:
Intrinsic Resistance to Gram-negative bacteria
(OM impermeability)

Problem-3:
Adaptive resistance
(Persister bacteria)



Harms, et al. Science 2016, 354, 6318

Problem-4:
Biofilms are resistant to antibiotics
(Diffusion barriers & metabolically repressed cells)



Lewis, Nat Rev Microbiol 2007, 5, 48

Problem-5:
Intracellular Infections
(Evasion from antibiotics & host immune response)

Challenges of Complicated Infections

Paramita et al. Med Chem Commun 2017, 8, 516 ; Conlon et al Nat Microbiol 2016, 1, 16051 10

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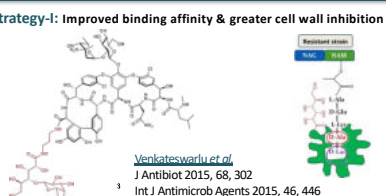
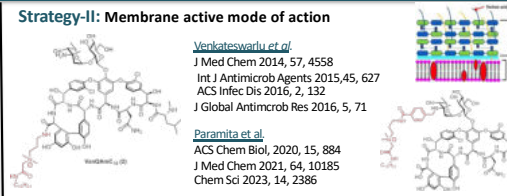
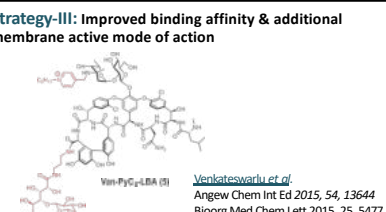
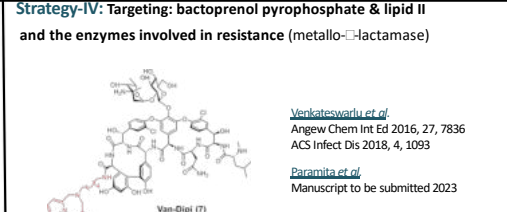
Glycopeptide Research: Contribution from other Scientists

MULTIVALENCY APPROACH				SYNTHETIC & SEMI-SYNTHETIC ANALOGS	PEPTIDE-BASED DERIVATIVES	SITE-SELECTIVE MODIFICATION OF VANCOMYCIN
						
K. C. Nicolau <i>Rice University</i>	G.M. Whitesides <i>Harvard University</i>	K. B. Sharpless <i> Scripps Institute</i>	Daisuke Uemura <i>Nagoya University</i>	Dale Boger <i>Scripps Institute</i>	Lynette Cegelski <i>Stanford University</i>	Scott J. Miller <i>Yale University</i>
<i>.....and many more!!</i>						
MEMBRANE-ANCHORING SEMISYNTHETIC DERIVATIVES	SIDEROPHORE-GLYCOPEPTIDE CONJUGATES	LIPIDATED SEMISYNTHETIC GLYCOPEPTIDES	VANCOMYCIN-POLYMYXIN NONAPEPTIDE CONJUGATES	TYPE V GLYCOPEPTIDE AGLYCONS		
						
Matthew Cooper <i>University of Queensland</i>	Marvin Miller <i>University of Notre Dame</i>	Hirokazu Arimoto <i>Tohoku University</i>	Nathaniel Martin <i>Leiden University</i>	Gerard D. Wright <i>MacMaster University</i>		

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Our Contribution: Novel class of semi-synthetic glycopeptides

<p>Strategy-I: Improved binding affinity & greater cell wall inhibition</p>  <p>Venkateswarlu et al. J Antibiob 2015, 68, 302 Int J Antimicrob Agents 2015, 46, 446</p>	<p>Strategy-II: Membrane active mode of action</p>  <p>Venkateswarlu et al. J Med Chem 2014, 57, 4558 Int J Antimicrob Agents 2015, 45, 627 ACS Infect Dis 2016, 2, 132 J Global Antimicrob Res 2016, 5, 71</p> <p>Paramita et al. ACS Chem Biol, 2020, 15, 884 J Med Chem 2021, 64, 10185 Chem Sci 2023, 14, 2386</p>
<p>Strategy-III: Improved binding affinity & additional membrane active mode of action</p>  <p>Venkateswarlu et al. Angew Chem Int Ed 2015, 54, 13644 Bioorg Med Chem Lett 2015, 25, 5477</p>	<p>Strategy-IV: Targeting: bactoprenol pyrophosphate & lipid II and the enzymes involved in resistance (metallo-β-lactamase)</p>  <p>Venkateswarlu et al. Angew Chem Int Ed 2016, 27, 7836 ACS Infect Dis 2018, 4, 1093</p> <p>Paramita et al. Manuscript to be submitted 2023</p>

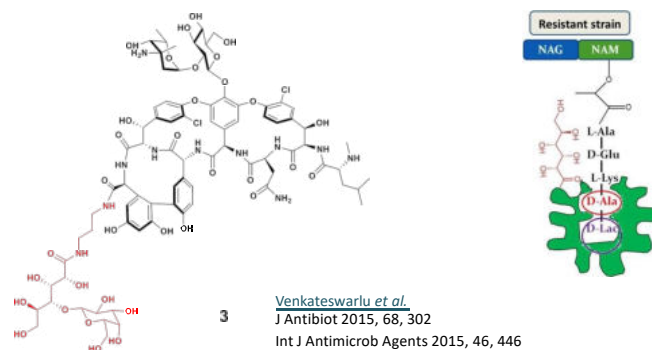
[Paramita et al.](#), Med Chem Commun 2017, 8, 516 (Review); Book: Antibiotic Drug Resistance (Book Chapter), John Wiley & Sons, Inc., 2019 [Geetika et al.](#) J Med Chem 2019, 62, 3184 (Perspective), [Yash et al.](#), Chem Commun, 2022, 58, 1881 (Feature Article), ACS Infect. Dis. 2022, 8, 1 (Review); Book: Alternative to Antibiotics (Book Chapter), Springer Link, 2022; **Patents: WO2013072838 , WO2016103284A1, WO2015040467A1**

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Our Contribution: Novel class of semi-synthetic glycopeptides

Strategy-I: Improved binding affinity & greater cell wall inhibition



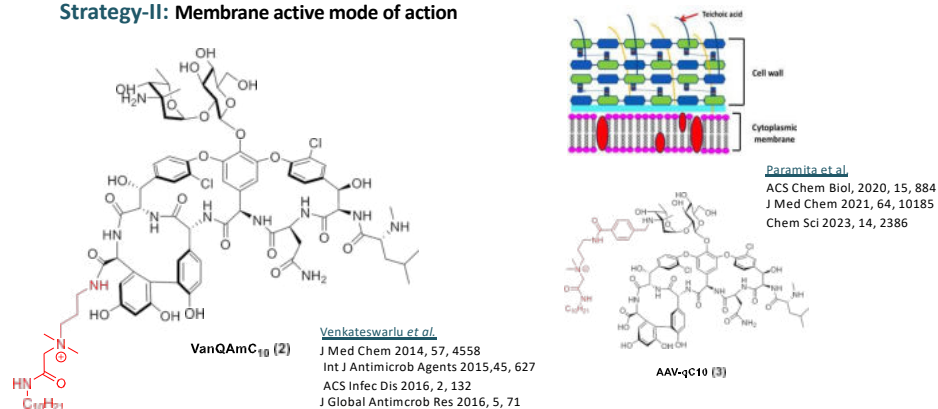
[Paramita et al.](#), Med Chem Commun 2017, 8, 516 (Review); Book: Antibiotic Drug Resistance (Book Chapter), John Wiley & Sons, Inc., 2019 [Geetika et al.](#) J Med Chem 2019, 62, 3184 (Perspective), [Yash et al.](#), Chem Commun, 2022, 58, 1881 (Feature Article), ACS Infect. Dis. 2022, 8, 1 (Review); Book: Alternative to Antibiotics (Book Chapter), Springer Link, 2022; Patents: WO2013072838, WO2016103284A1, WO2015040467A1

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Our Contribution: Novel class of semi-synthetic glycopeptides

Strategy-II: Membrane active mode of action



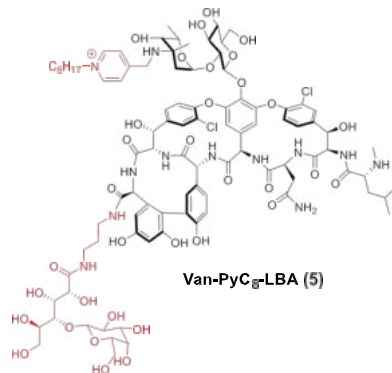
[Paramita et al.](#), Med Chem Commun 2017, 8, 516 (Review); Book: Antibiotic Drug Resistance (Book Chapter), John Wiley & Sons, Inc., 2019 [Geetika et al.](#) J Med Chem 2019, 62, 3184 (Perspective), [Yash et al.](#), Chem Commun, 2022, 58, 1881 (Feature Article), ACS Infect. Dis. 2022, 8, 1 (Review); Book: Alternative to Antibiotics (Book Chapter), Springer Link, 2022; Patents: WO2013072838, WO2016103284A1, WO2015040467A1

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Our Contribution: Novel class of semi-synthetic glycopeptides

Strategy-III: Improved binding affinity & additional membrane active mode of action



[Venkateswarlu *et al.*](#)
 Angew Chem Int Ed 2015, 54, 13644
 Bioorg Med Chem Lett 2015, 25, 5477

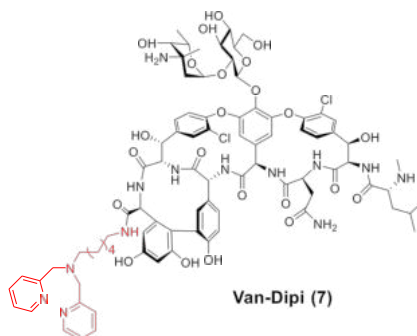
[Paramita *et al.*](#), Med Chem Commun 2017, 8, 516 (Review); Book: Antibiotic Drug Resistance (Book Chapter), John Wiley & Sons, Inc., 2019 [Geetika *et al.*](#) J Med Chem 2019, 62, 3184 (Perspective), [Yash *et al.*](#) Chem Commun, 2022, 58, 1881 (Feature Article), ACS Infect. Dis. 2022, 8, 1 (Review); Book: Alternative to Antibiotics (Book Chapter), Springer Link, 2022; Patents: WO2013072838, WO2016103284A1, WO2015040467A1

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Our Contribution: Novel class of semi-synthetic glycopeptides

Strategy-IV: Targeting: bactoprenol pyrophosphate & lipid II and the enzymes involved in resistance (metallo-β-lactamase)



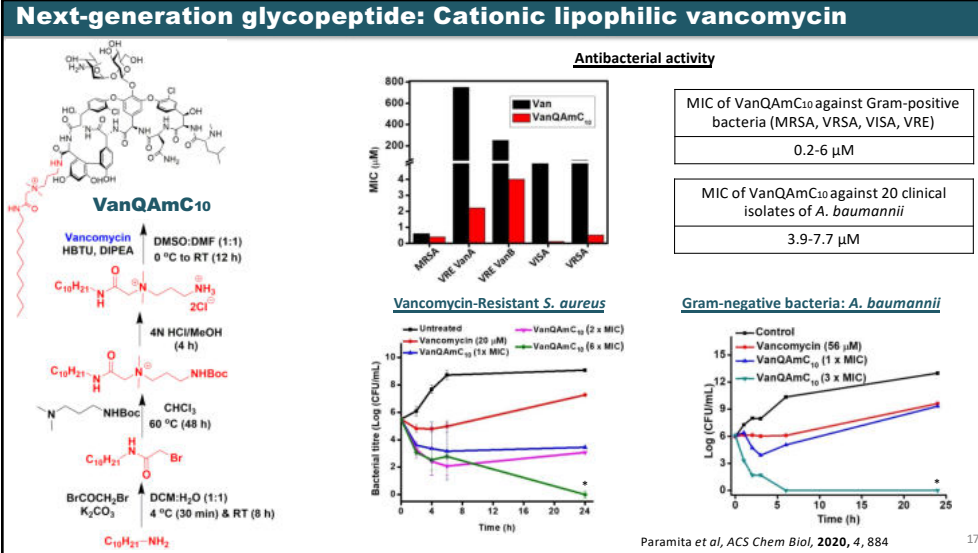
[Venkateswarlu *et al.*](#)
 Angew Chem Int Ed 2016, 27, 7836
 ACS Infect Dis 2018, 4, 1093

[Paramita *et al.*](#)
 Manuscript to be submitted 2023

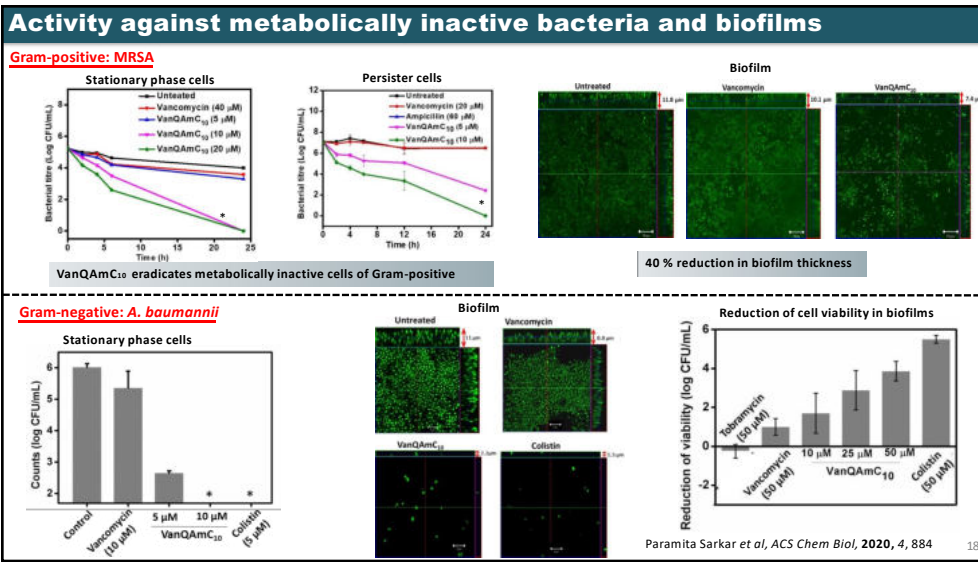
[Paramita *et al.*](#), Med Chem Commun 2017, 8, 516 (Review); Book: Antibiotic Drug Resistance (Book Chapter), John Wiley & Sons, Inc., 2019 [Geetika *et al.*](#) J Med Chem 2019, 62, 3184 (Perspective), [Yash *et al.*](#) Chem Commun, 2022, 58, 1881 (Feature Article), ACS Infect. Dis. 2022, 8, 1 (Review); Book: Alternative to Antibiotics (Book Chapter), Springer Link, 2022; Patents: WO2013072838, WO2016103284A1, WO2015040467A1

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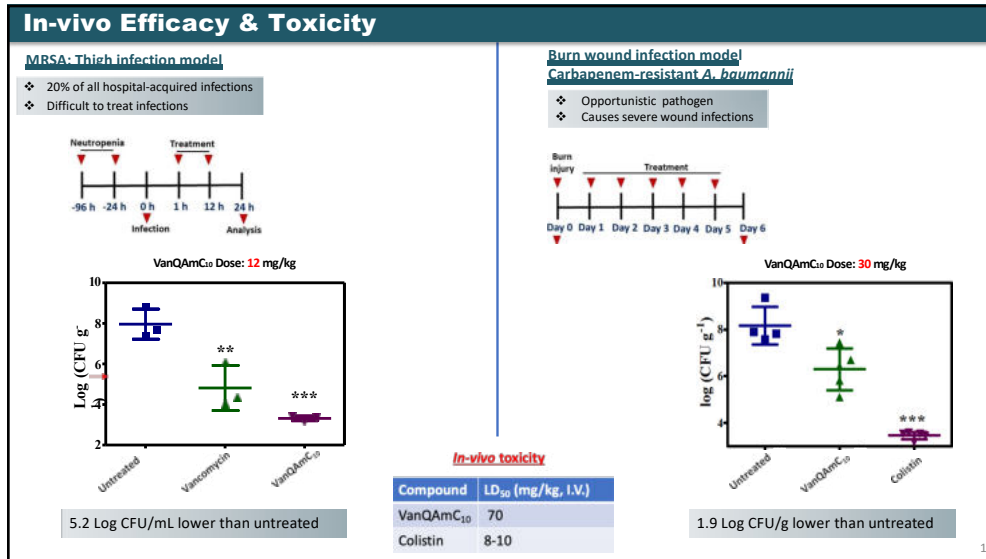
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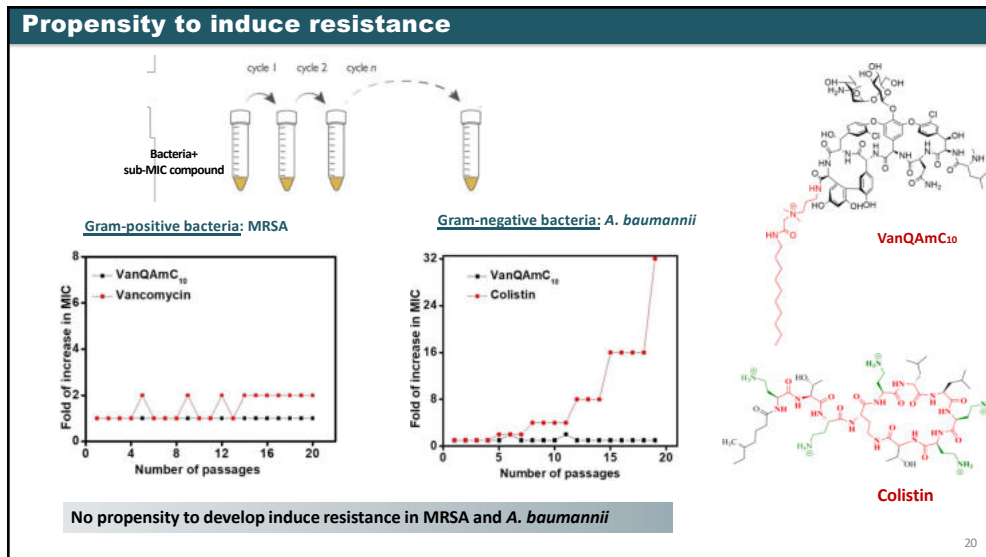
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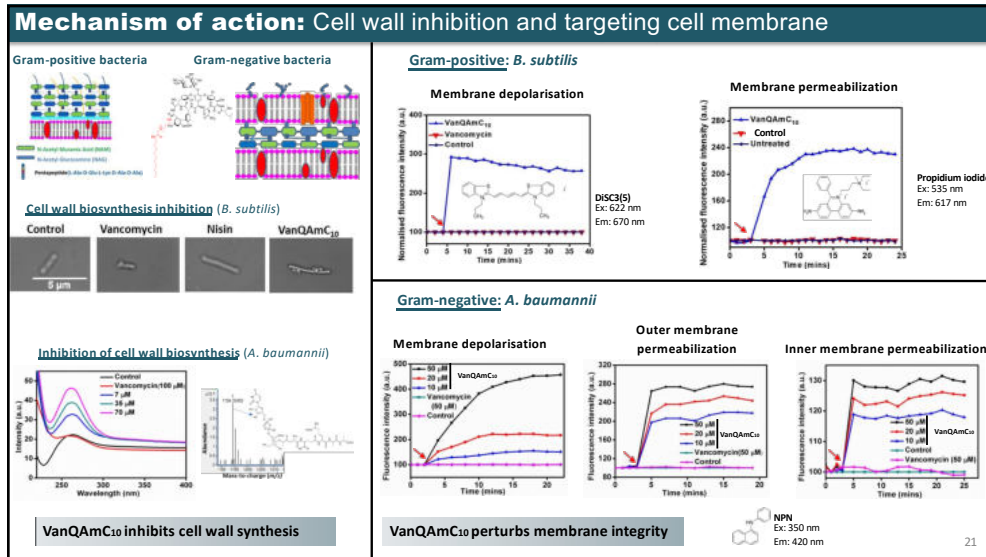
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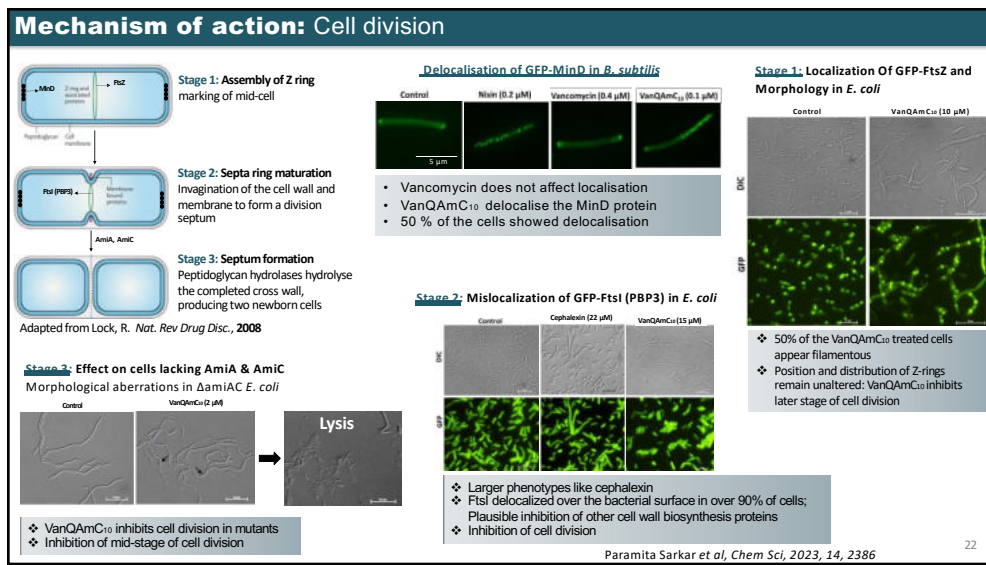
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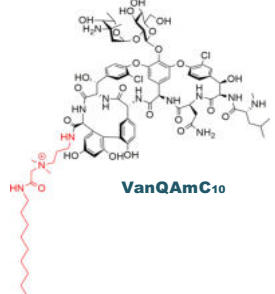
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Summary

New insights into mechanisms of action of membrane active vancomycin derivatives



VanQA mC-10

MULTIPLE MECHANISMS OF ACTION

1) Inhibition of cell wall biosynthesis

ADDITIONAL MECHANISMS:

2) Inhibition of cell division

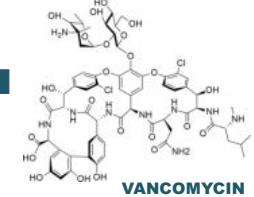
a) Membrane-depolarisation

b) Membrane-permeabilization

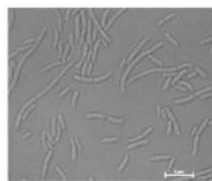
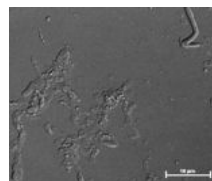
c) Delocalisation of MinD

d) Delocalisation of FtsI (PBP3)

3) Induces autophagy (Xenophagy)



VANCOMYCIN

Paramita Sarkar *et al*, *Chem. Sci*, **2023**, 14, 2386.

Paramita Sarkar *et al*, *ACS Chem Biol*, **2020**, 4, 884.

- ❖ Active against vancomycin-resistant Gram-positive bacteria (VRSA, VRE)
- ❖ Active against Gram-negative bacteria
- ❖ No propensity to induce resistance
- ❖ Active against stationary, persister cells and biofilm
- ❖ Showed good in-vivo activity with minimum toxicity

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Acknowledgement



Past Members

Dr. Venkateswarlu Y
 Dr. Divakara S.S.M. Uppu
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 Dr. Mohini Mohan Konai
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 Dr. Brinta Bhattacharjee
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- Prof. Julia Bandow, Ruhr University Bochum, Germany
- Dr. Sidharth Chopra, CDRI
- Prof. Ravi Manjithaya, JNCASR



JNCASR



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Department of Bio Technology, Government of India



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COVID-19



ERIC



RAK-CAM



Public Health England



BRNS



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Thank You All

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Macrogenomic Engineering: Designing Proteins That Sense Chromatin Signals and Regulate Genes

Karmella A. Haynes, PhD

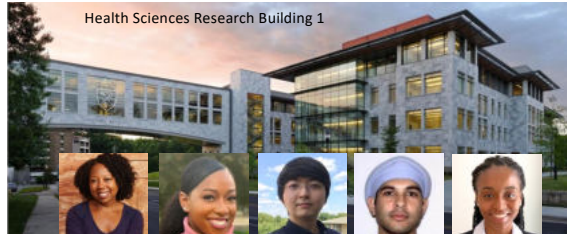
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1

Haynes Lab: Epigenetic Chromatin Engineering

Health Sciences Research Building 1



Karmella Haynes
PI/ Chief Architect



Kierra Franklin
BME PhD student



Seong Hu Kim
BME PhD student



Ranjit Pella
GMB PhD student



Ashley Townsel
CB PhD student



Greg Wu
UG Researcher



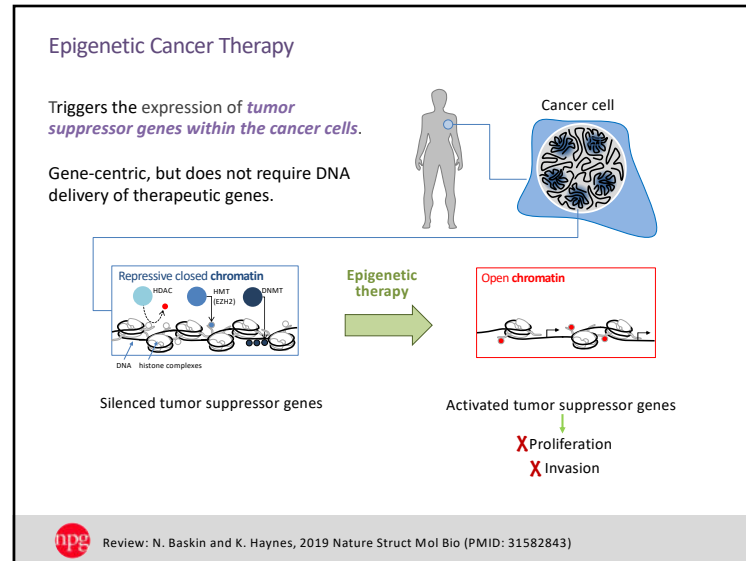
Jedidah Titus
UG Researcher



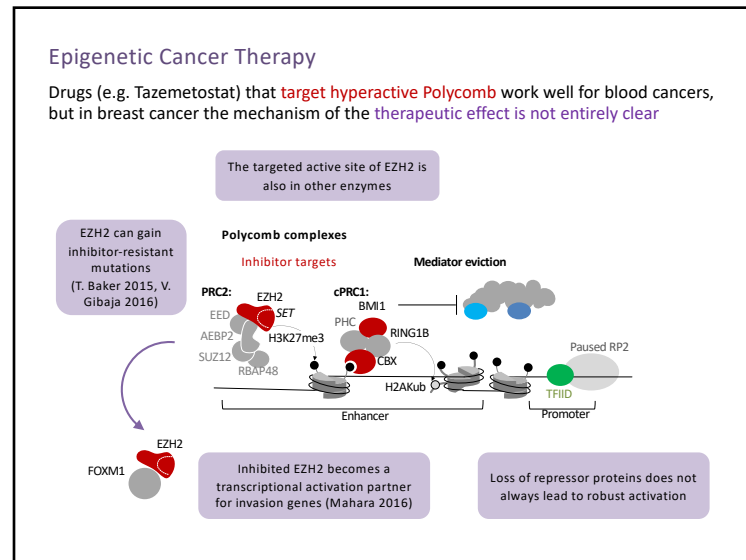
khayneslab.wordpress.com

Dr. Karmella Haynes, PhD

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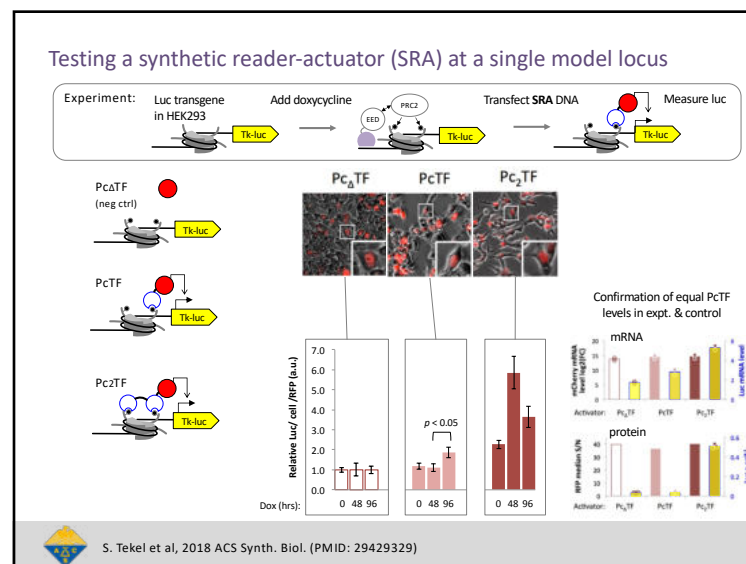


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Can we build a synthetic, functional reader-effector?

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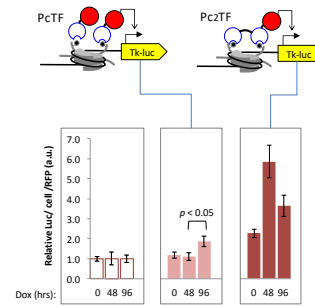
Testing a synthetic reader-actuator (SRA) at a single model locus

What did we learn about reader-effector design?

Functional RE's can be streamlined
(PcTF = 55 kD)

Affinity/ avidity matters:

- Monovalent PcTF has a higher stoichiometry of **activator** to target.
- But **bivalent** PcTF is a stronger activator.
- Therefore, enhanced affinity/ avidity (per molecule) has more impact for RE function effector stoichiometry.



S. Tekel et al, 2018 ACS Synth. Biol. (PMID: 29429329)

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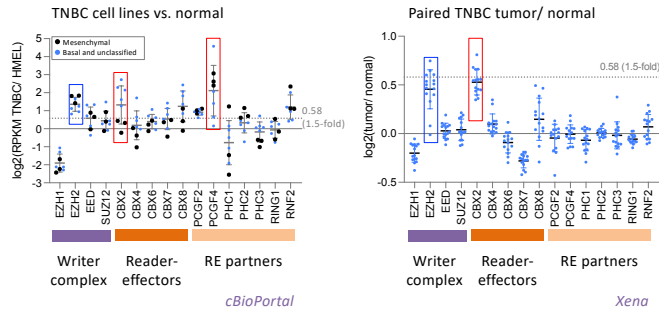
What happens when we unleash a synthetic reader-effector onto a natural epigenome?

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Reader-Effector Chromatin Proteins are Misregulated in Triple Negative Breast Cancer

Polycomb expression levels (RNA-seq)

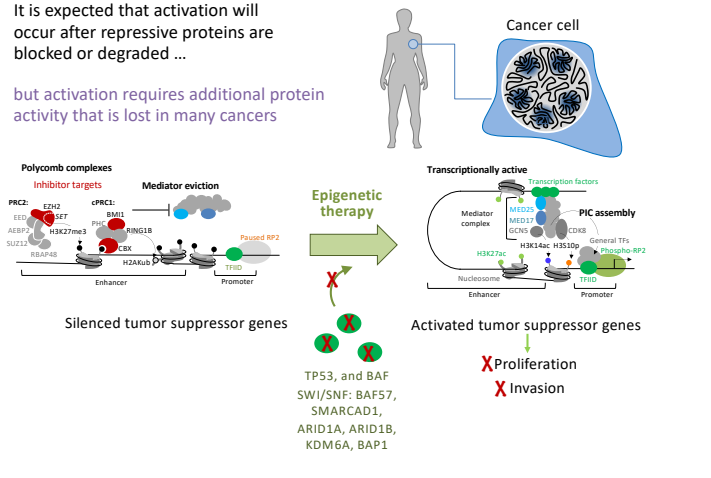


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The Problem with Epigenetic Therapy for Cancer Treatment and Research

It is expected that activation will occur after repressive proteins are blocked or degraded ...

but activation requires additional protein activity that is lost in many cancers

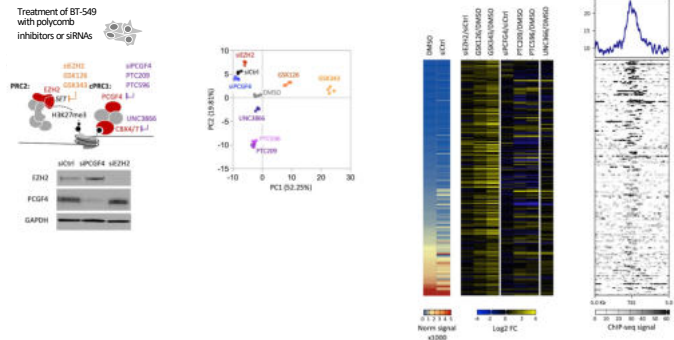


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The Problem with Epigenetic Therapy for Cancer Treatment and Research

Standard polycomb-targeting approaches show inconsistent effects on transcription levels lowly and highly-expressed genes.

Gene expression profiling

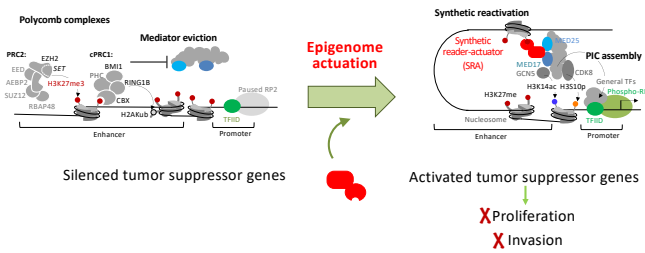


GEN Biotechnology L. Hong et al, 2023 GEN Biotech, <https://www.liebertpub.com/doi/10.1089/genbio.2023.0020>

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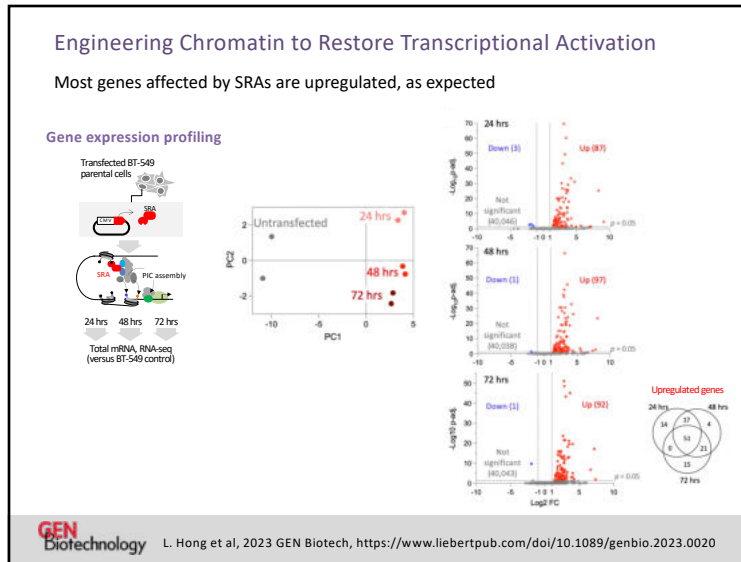
Engineering Chromatin to Restore Transcriptional Activation

OUR APPROACH: Epigenome actuation
To develop a better tool to study how reactivation blocks cancer, we design proteins that target repressed chromatin and activate gene expression

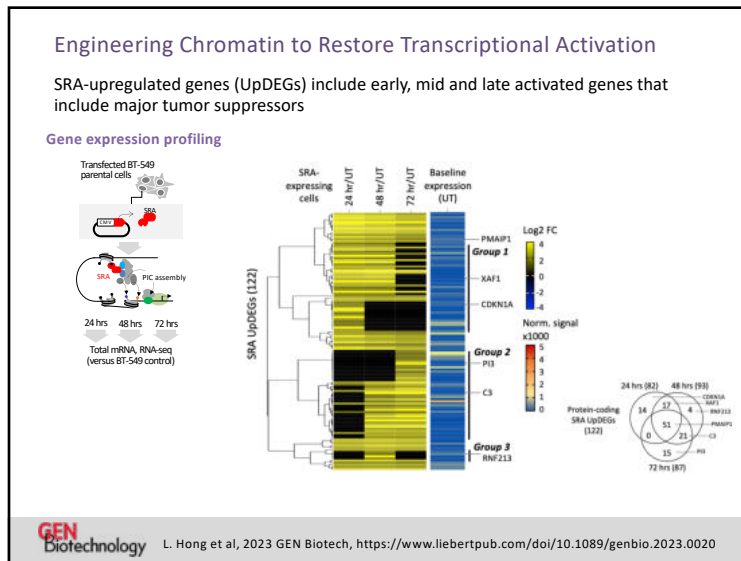


GEN Biotechnology L. Hong et al, 2023 GEN Biotech, <https://www.liebertpub.com/doi/10.1089/genbio.2023.0020>

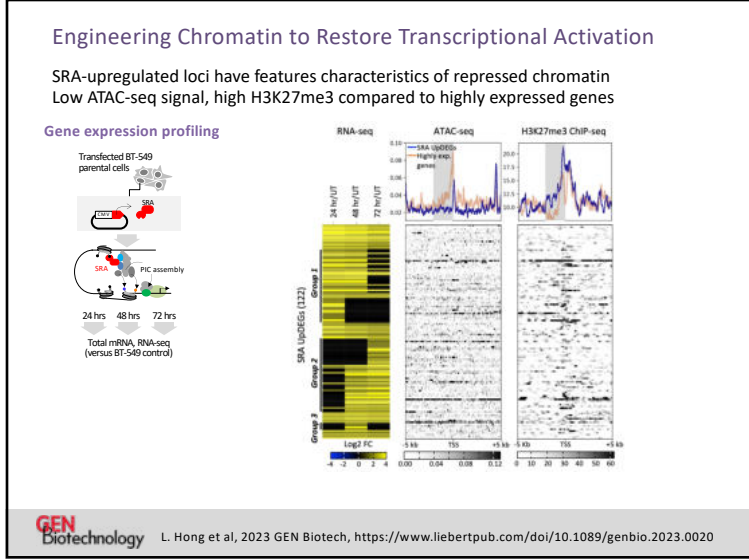
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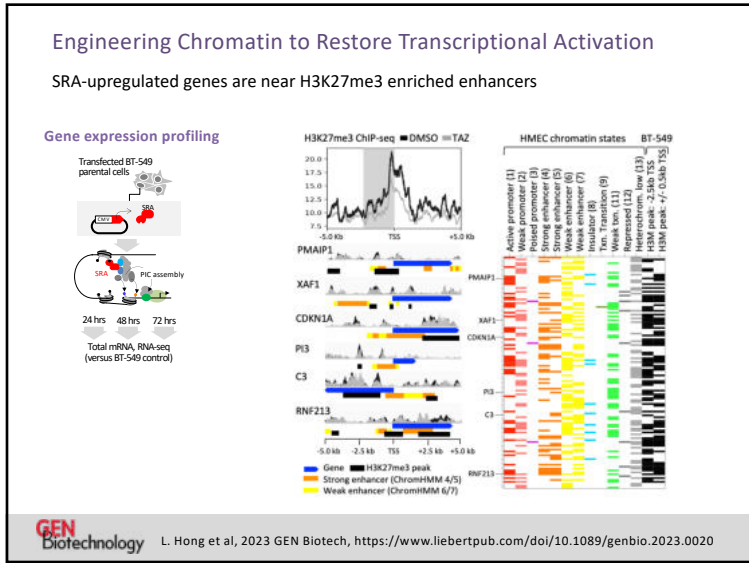
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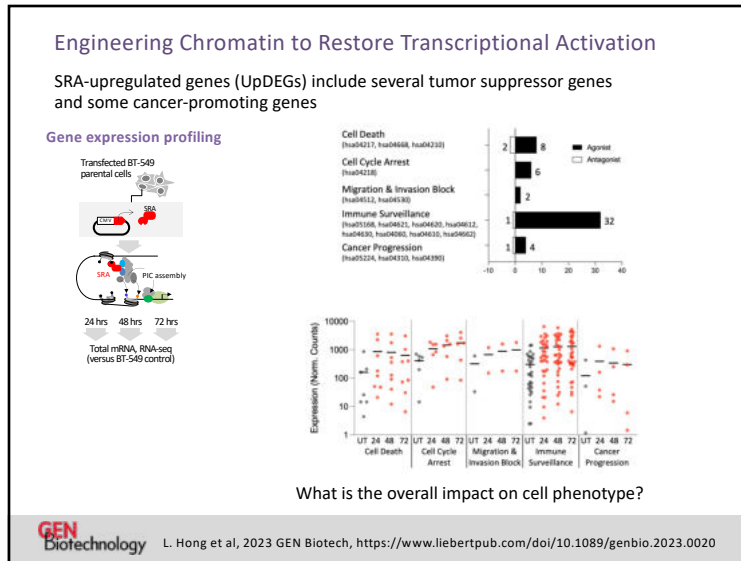
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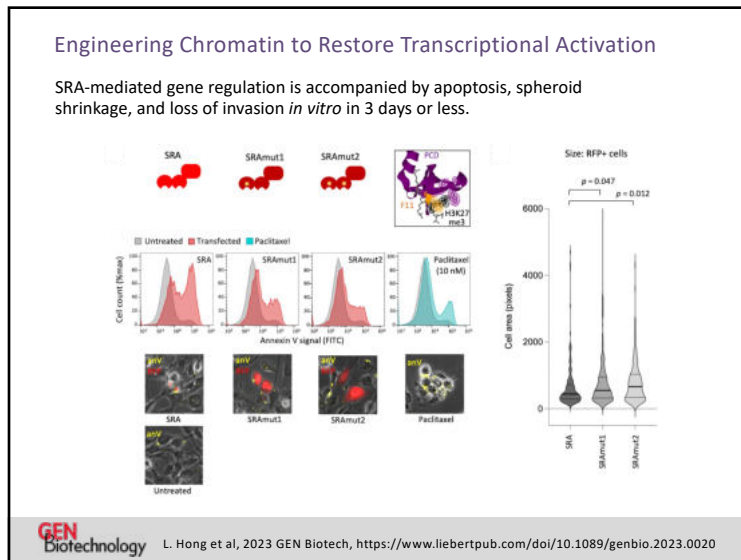
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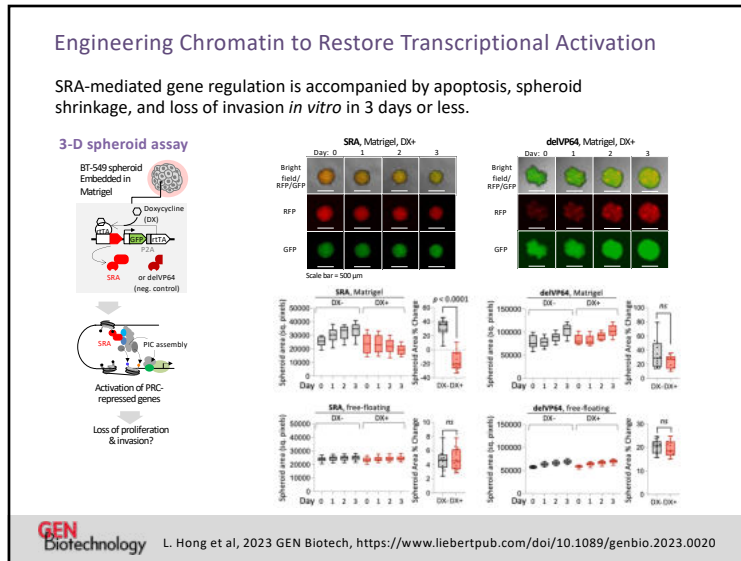
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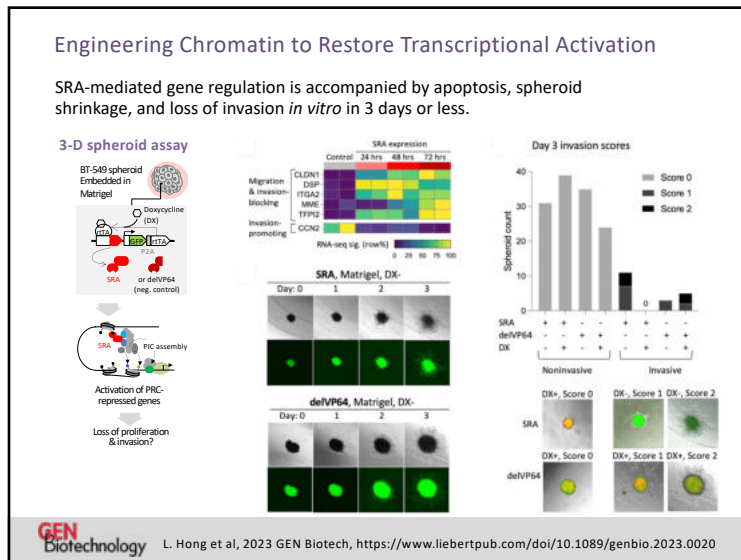
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