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Cutting Edge Antibiotic and Gene Therapy Research

JAYANTA HALDAR, PHD
Editor-in-Chief, ACS Infectious Diseases and International Publisher, New Chemistry Unit
Senior Associate Publisher, American Chemical Society

KARMELLA A. HAYNES, PHD
Associate Editor, ACS Synthetic Biology and Technical Publisher, 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

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National Chemistry Week, ACS Webinar, October 18, 2023

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
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.

Vancomycin: A natural glycopeptide antibiotic

- **Isolated:** from soil bacterium
  *Amycolatopsis orientalis* in 1952

- **Approved:** FDA 1958

Vancomycin

- **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
Clinically approved Semi-synthetic glycopeptides

**TELAVANCIN**
- Approved in 2009
- Complicated skin and skin-structure infections (cSSSi)
- Hospital-acquired and ventilator-associated pneumonia caused by *S. aureus*, enterococci & streptococci.

**DALBAVANCIN**
- Approved in 2014
- Acute skin and skin-structure infections caused by methicillin-susceptible and resistant *S. aureus* (MSSA, MRSA), Streptococci and vancomycin sensitive *E. faecalis*

**ORITAVANCIN**
- Approved in 2014
- Acute skin and tissue infections caused by MRSA, MSSA, Streptococci and vancomycin-susceptible *E. faecalis*


---

**Cell Wall (Peptidoglycan) Biosynthesis**

Varki A et al. *Essential of Glycobiology*

Transporters/Flippases: FtsW, Muri, AMI

Paramita et al. *Med Chem Commun* 2017, 8, 516
**Vancomycin: Mechanism of action**

- Vancomycin is a cell wall biosynthesis inhibitor.
- It binds to D-alanyl-D-alanine (D-ala-D-ala) residues on the end of the growing peptidoglycan chain.
- This prevents the peptidoglycan chains from cross-linking, which weakens the cell wall and makes the bacterium more susceptible to lysis.

**Concern of vancomycin resistant bacteria: Acquired resistance**

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

- **Original strain**
  - D-Ala-D-Ala
  - \( K_a = 1.3 \times 10^9 \text{ M}^{-1} \)

- **Resistant strain**
  - D-Ala-D-Lac
  - \( K_a = 5 \times 10^7 \text{ M}^{-1} \)

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

- The binding constant decreases by ~1,000 fold.
- The antibacterial activity decreases by more than 100–1,000 fold.

Gram-negative bacteria: Inherent resistance to vancomycin

- Gram-Positive Bacteria (Staphylococcus aureus, Enterococcus faecium)
- Gram-Negative Bacteria (Escherichia coli, Pseudomonas aeruginosa)

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).

Challenges associated with bacterial infections & Drug resistance

- Problem-1: Acquired resistance (VISA, VRSA & VRE)
- Problem-2: Intrinsic Resistance to Gram-negative bacteria (OM impermeability)
- Problem-3: Adaptive resistance (Persister bacteria)
- Problem-4: Biofilms are resistant to antibiotics (Diffusion barriers & metabolically repressed cells)
- Problem-5: Intracellular infections (Evasion from antibiotics & host immune response)

References:
- Varki A et al. Essential of Glycobiology (Book)
- Christopher Walsh, Antibiotics: Actions, Origin, Resistance (Book)
- Lewis, Nat Rev Microbiol 2007, 5, 48
- Paramita et al. Med Chem Commun 2017, 8, 516; Canton et al. Nat Microbial 2016, 1, 16051
Glycopeptide Research: Contribution from other Scientists

- **Multivalency Approach**
  - K. C. Nicolaou (Rice University)
  - G. M. Whitesides (Harvard University)
  - Daisuke Shimura (Nagoya University)

- **Synthetic & Semi-Synthetic Analogues**
  - Dale Boger (Scripps Institute)
  - Lynette Cagasaki (Stanford University)
  - Scott J. Miller (Yale University)

- **Peptide-Based Derivatives**
  - Matthew Cooper (University of Queensland)
  - Hirokazu Arimoto (Tohoku University)
  - Nathaniel Martin (Leiden University)
  - Gerard D. Wright (MacMaster University)

- **Membrane-Anchoring Semisynthetic Derivatives**
  - Marvin Miller (University of Notre Dame)

- **Siderophore-Glycopeptide Conjugates**
  - Matthew Cooper (University of Queensland)

- **Vancomycin-Polymyxin Nonapeptide Conjugates**
  - Matthew Cooper (University of Queensland)

- **Type V Glycopeptide Aglycons**
  - Matthew Cooper (University of Queensland)

- **Site-Selective Modification of Vancomycin**
  - Matthew Cooper (University of Queensland)

- **and many more!!**

**Our Contribution: Novel class of semi-synthetic glycopeptides**

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

**Strategy-II:** Membrane active mode of action

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

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

*References*
- Venkateswarlu et al. J Med Chem 2014, 57, 4048
- Int. J Antimicrob Agents 2015, 45, 627
- ACS Infect Dis 2016, 2, 132
- Global Antimicrob Res 2016, 5, 71

*Preprints*
- ACS Chem Biol 2020, 15, 884
- J Med Chem 2022, 65, 10385
- Chem Sci 2023, 14, 2386

*Patents*
- WO2013072838
- WO201610284A1
- WO201504067A1

*Review Papers*
- Med Chem Commun 2017, 8, 516
- J Med Chem 2019, 62, 1181 (Perspective)
- ACS Infect Dis. 2016, 2, 132
- Global Antimicrob Res 2016, 5, 71
- ACS Chem Biol, 2020, 15, 884
- J Med Chem 2021, 64, 10185
- Chem Sci 2023, 14, 2386
- Manuscript to be submitted 2023
Our Contribution: Novel class of semi-synthetic glycopeptides

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

Venkateswarlu et al. J Antibiot 2015, 68, 302
Int J Antimicrob Agents 2015, 46, 446

Strategy-II: Membrane active mode of action


Our Contribution: Novel class of semi-synthetic glycopeptides

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

Our Contribution: Novel class of semi-synthetic glycopeptides

Strategy-IV: Targeting: bactoprenol pyrophosphate & lipid II and the enzymes involved in resistance (metallo-\beta-lactamase)
**Next-generation glycopeptide: Cationic lipophilic vancomycin**

**Antibacterial activity**

- MIC of VanQAmC10 against Gram-positive bacteria (MRSA, VRSA, VISA, VRE)
  - 0.2-6 μM
- MIC of VanQAmC10 against 20 clinical isolates of A. baumannii
  - 3.9-7.7 μM

**Vancomycin-Resistant S. aureus**

**Gram-negative bacteria: A. baumannii**

**Activity against metabolically inactive bacteria and biofilms**

**Gram-positive: MRSA**

- Stationary phase cells
- Persistor cells
- Biofilm

**Gram-negative: A. baumannii**

- Stationary phase cells
- Biofilm

Paramita et al, ACS Chem Biol, 2020, 4, 884
**In-vivo Efficacy & Toxicity**

**MRSA: Thigh infection model**
- 20% of all hospital-acquired infections
- Difficult to treat infections

**Burn wound infection model**
- Carbapenem-resistant A. baumannii
- Opportunistic pathogen
- Causes severe wound infections

**MRSA: Thigh infection model**
- VanQAmC dose: 32 mg/kg
- 5.2 log CFU/mL lower than untreated

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD50 (mg/kg, i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VanQAmC</td>
<td>70</td>
</tr>
<tr>
<td>Colistin</td>
<td>8-30</td>
</tr>
</tbody>
</table>

**Burn wound infection model**
- VanQAmC dose: 30 mg/kg
- 1.9 log CFU/g lower than untreated

**Propensity to induce resistance**

- **Gram-positive bacteria: MRSA**
  - VanQAmC
  - Vancomycin
- **Gram-negative bacteria: A. baumannii**
  - VanQAmC
  - Colistin

**No propensity to develop induce resistance in MRSA and A. baumannii**
**Mechanism of action: Cell wall inhibition and targeting cell membrane**

- **Gram-positive bacteria**
  - **Gram-negative bacteria**
  - Cell wall biosynthesis inhibition
    - 535 nm Ex: 535 nm Em: 617 nm
    - DiSC3(5)
    - Membrane depolarisation
    - Membrane permeabilization
    - NPN
      - Ex: 350 nm Em: 420 nm

- **VanQAmC10** inhibits cell wall synthesis

- **Inhibition of cell wall biosynthesis**
  - A. baumannii
  - B. subtilis

**Mechanism of action: Cell division**

- Stage 1: Assembly of Z-ring
  - Marking of mid-cell

- Stage 2: Septa ring maturation
  - Invagination of the cell wall and membrane to form a division septum

- Stage 3: Septum formation
  - Peptidoglycan hydrolases hydrolyse the completed cross wall, producing two newborn cells

- **Lysis**
  - VanQAmC10 inhibits cell division in mutants
  - Inhibition of mid-stage of cell division

- *Adapted from Lock, R. Nat. Rev Drug Disc., 2008*
  - Paramita Sarkar et al, Chem Sci, 2023, 14, 2386
New insights into mechanisms of action of membrane active vancomycin derivatives

**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)

- 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


**Summary**

**Acknowledgement**

**Past Members**
- Dr. Venkateswarlu
- Dr. Dukara S.S.M. Uppu
- Dr. Chandrudhish Ghosh
- Dr. Jaiul Hoque
- Dr. Mohini-Mohan Konai
- Dr. Paramita Sarkar
- Dr. Swagatam Barman
- Dr. Binti Bhattacherjee
- Dr. Sandip Samaddar
- Dr. Padma Akappadali
- Ms. Sowdham B. Manjusarith
- Dr. Pratik Kumar
- Mr. Utsarga Adhikary
- Ms. Shanola S. Sequeira
- Dr. Spandhana Gunuguntala
- Dr. Roys Mukharjee
- Dr. Debojyoti Baner

**Collaborators**
- Prof. Richa Priyadarshini, Shiv Nadar University
- Prof. Julia Bandow, Ruhr University Bochum, Germany
- Dr. Sidharth Chopra, CDRI
- Prof. Ravi Manjithaya, JNCASR

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

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Haynes Lab: Epigenetic Chromatin Engineering
Health Sciences Research Building 3
Epigenetic Cancer Therapy

Triggers the expression of tumor suppressor genes within the cancer cells.

Gene-centric, but does not require DNA delivery of therapeutic genes.

Repressive closed chromatin

Epigenetic therapy

Open chromatin

Silenced tumor suppressor genes

Activated tumor suppressor genes

X Proliferation

X Invasion


Epigenetic Cancer Therapy

Drugs (e.g. Tazemetostat) that target hyperactive Polycomb work well for blood cancers, but in breast cancer the mechanism of the therapeutic effect is not entirely clear.

The targeted active site of EZH2 is also in other enzymes.

EZH2 can gain inhibitor-resistant mutations. (T. Baker 2015, V. Gibaja 2016)

Polycomb complexes

Inhibitor targets

Mediator eviction

Inhibited EZH2 becomes a transcriptional activation partner for invasion genes (Mahara 2016)

Loss of repressor proteins does not always lead to robust activation
Epigenetic Engineering

A restorative approach: Can we install engineered chromatin components to understand chromatin’s direct impact on epigenetic reprogramming of cancer?

Significance: Reader-Effector Proteins are Mutated/ Misregulated in Neurological, Immune, and Cardiovascular Disorders and Cancer

Cancer: solid and blood cancers

Neurological: Rett syndrome, autism, epilepsy

Immune: severe combined immunodeficiency (SCID), Omenn syndrome, systemic lupus erythematosus

Cardiovascular disease
Can we build a synthetic, functional reader-effector?

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.

What happens when we unleash a synthetic reader-effector onto a natural epigenome?
Reader-Effector Chromatin Proteins are Misregulated in Triple Negative Breast Cancer

Polycomb expression levels (RNA-seq)

Pair of TNBC tumor/normal

log2(tumor/normal)

0.58 (1.5-fold)

Paired TNBC tumor/normal

log2(RPKM TNBC/HMEL)

Mesenchymal

Basal and unclassified

Reader-effectors

Writer complex

RE partners

cBioPortal

Xena

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

Epigenetic therapy

Silenced tumor suppressor genes

Activated tumor suppressor genes

TP53, and BAF

SWI/SNF: BAF57, SMARCA1, ARID1A, ARID1B, KDM6A, BAP1

Promotion

Invasion
The Problem with Epigenetic Therapy for Cancer Treatment and Research

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

Gene expression profiling

Treatment of BT-549 cells with polycomb inhibitors or siRNAs

The Problem with Epigenetic Therapy for Cancer Treatment and Research

Gene expression profiling

Treatment of BT-549 with polycomb inhibitors or siRNAs

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

Silenced tumor suppressor genes

Activated tumor suppressor genes

* Proliferation
  * Invasion

**Epigenome actuation**

Synthetic reactivation

Enhancer Promoter

CPC complexes

Mediator eviction

PcG complexes

Enhancer

Promoter
Engineering Chromatin to Restore Transcriptional Activation

Most genes affected by SRAs are upregulated, as expected

Gene expression profiling

SRA-upregulated genes (UpDEGs) include early, mid and late activated genes that include major tumor suppressors

Gene expression profiling
Engineering Chromatin to Restore Transcriptional Activation

SRA-upregulated loci have features characteristics of repressed chromatin
Low ATAC-seq signal, high H3K27me3 compared to highly expressed genes

Gene expression profiling

Transfected BT-549 parental cells

PIC assembly

SRA

Total mRNA, RNA-seq
(versus BT-549 control)

CMV

SRA

48 hrs 72 hrs

Engineering Chromatin to Restore Transcriptional Activation

SRA-upregulated genes (UpDEGs) include several tumor suppressor genes and some cancer-promoting genes.

Gene expression profiling

SRA-mediated gene regulation is accompanied by apoptosis, spheroid shrinkage, and loss of invasion in vitro in 3 days or less.

What is the overall impact on cell phenotype?

Engineering Chromatin to Restore Transcriptional Activation

SRA-mediated gene regulation is accompanied by apoptosis, spheroid shrinkage, and loss of invasion in vitro in 3 days or less.

3-D spheroid assay


Engineering Chromatin to Restore Transcriptional Activation

SRA-mediated gene regulation is accompanied by apoptosis, spheroid shrinkage, and loss of invasion in vitro in 3 days or less.

3-D spheroid assay

Acknowledgements

Haynes Lab @Emory
Dr. Natacia Williams
Lauren Hong
Dr. Cara Shields
Maya Jaffe

Haynes Lab @ASU
Dr. Stefan Tekel
Daniel Vargas

Funding

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