

Computational Framework for Understanding Microbial Pathogenesis and Antimicrobial Resistance (AMR)

Molecular biology and basic cellular physiology (24AIM112)
Ethics, innovative research, businesses & IPR (24AIM115)

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Introduction

Antimicrobial Resistance (AMR):

- AMR is when microbes resist drugs, making infections harder to treat.
- Understanding the genetic mechanisms behind host-pathogen interactions and AMR is crucial for developing effective prevention and treatment strategies.
- Our project focuses on analyzing gene sequences to uncover insights that can aid in combating infections.

Objective

- Predict Antimicrobial Resistance (AMR)
- Study Host-Pathogen Interactions
- Apply Machine Learning for Predictions
- Provide a Scalable and Cost-Effective Approach

Literature review

1. Prediction of antimicrobial resistance based on whole-genome sequencing and machine learning

- Demonstrated SVM, CNN models can effectively predict AMR with label encoding, one-hot encoding and frequency matrix chaos game representation (FCGR encoding) on whole-genome sequencing data, identify mutations that are associated with AMR for each antibiotic.

2. Machine learning-enabled prediction of antimicrobial resistance in foodborne pathogens

- Application of ML combined with WGS and spectroscopy techniques to identify and predict AMR in foodborne pathogens which is crucial to assure food safety

3. Ethics and antibiotic resistance

- the ethical challenges posed by antibiotic resistance, emphasizing the severe and unevenly distributed health consequences. It critiques common frameworks like patient responsibility, the tragedy of the commons, and antibiotic stewardship, highlighting their limitations

Literature review

4. Towards routine employment of computational tools for antimicrobial resistance determination via high-throughput sequencing

- It highlights advancements in bioinformatics pipelines, database improvements, and automation to enhance AMR prediction. The study emphasizes the need for standardization and routine implementation to improve clinical and public health responses.

5. Balancing the risks and benefits of antibiotic use in a globalized world: the ethics of antimicrobial resistance

- Addressing AMR's ethical dimensions includes fair resource allocation, environmental impact, and conflicts of interest in antibiotic development. Equitable access to antibiotics and stakeholder collaboration in stewardship are crucial to ensure public interest and responsible use. Balancing risks and benefits demands innovative, global strategies to preserve antibiotic efficacy for future generations.

Computational aspects to be used

- Data Retrieval & Preprocessing
UniProt, CARD, VFDB (Virulence Factor Database), STRING, KEGG
- Sequence Alignment & Similarity Search
BLASTp, Clustal Omega
- Host-Pathogen Interaction Prediction
STRING, ClusPro, KEGG pathway mapping
- Molecular Docking & Structural Analysis
SwissDock, PyMOL for protein-ligand interaction
Python (Biopython, Pandas, Scikit-learn)

AMR Gene Detection Menu:

1. Analyze sequences from CSV
2. Analyze single sequence
3. Exit

Enter choice (1-3): 2

Enter DNA sequence: ATGAAGTTAGGGCAACCCAG

Detected Resistance Genes:

Gene: vanA

Type: Vancomycin Resistance

Position: 0-20

Sequence: ATGAAGTTAGGGCAACCCAG

Similarity: 1.0

Fig. Output obtained from the draft Model trained for AMR Prediction

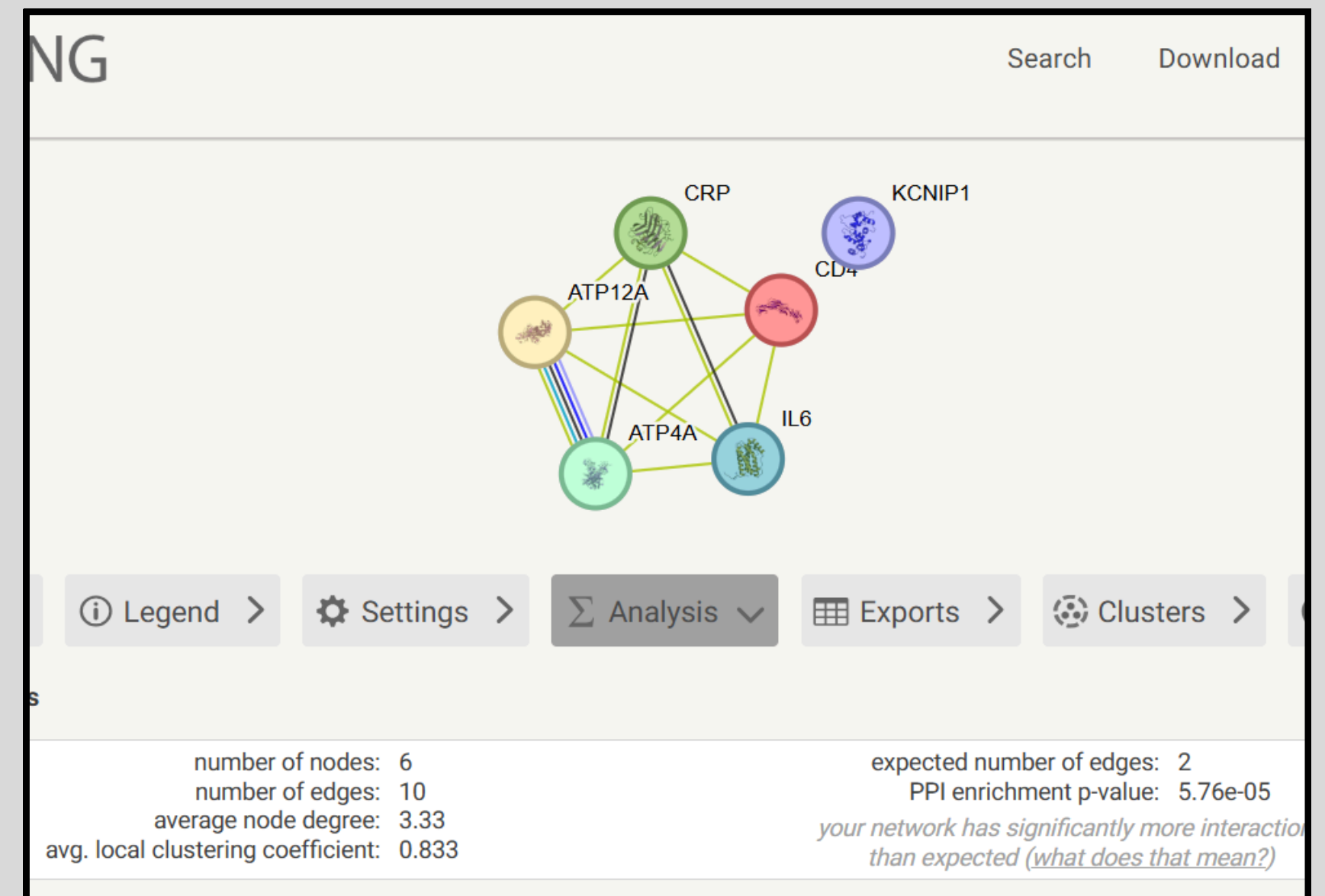


Fig. Output obtained from STRING: functional protein association networks

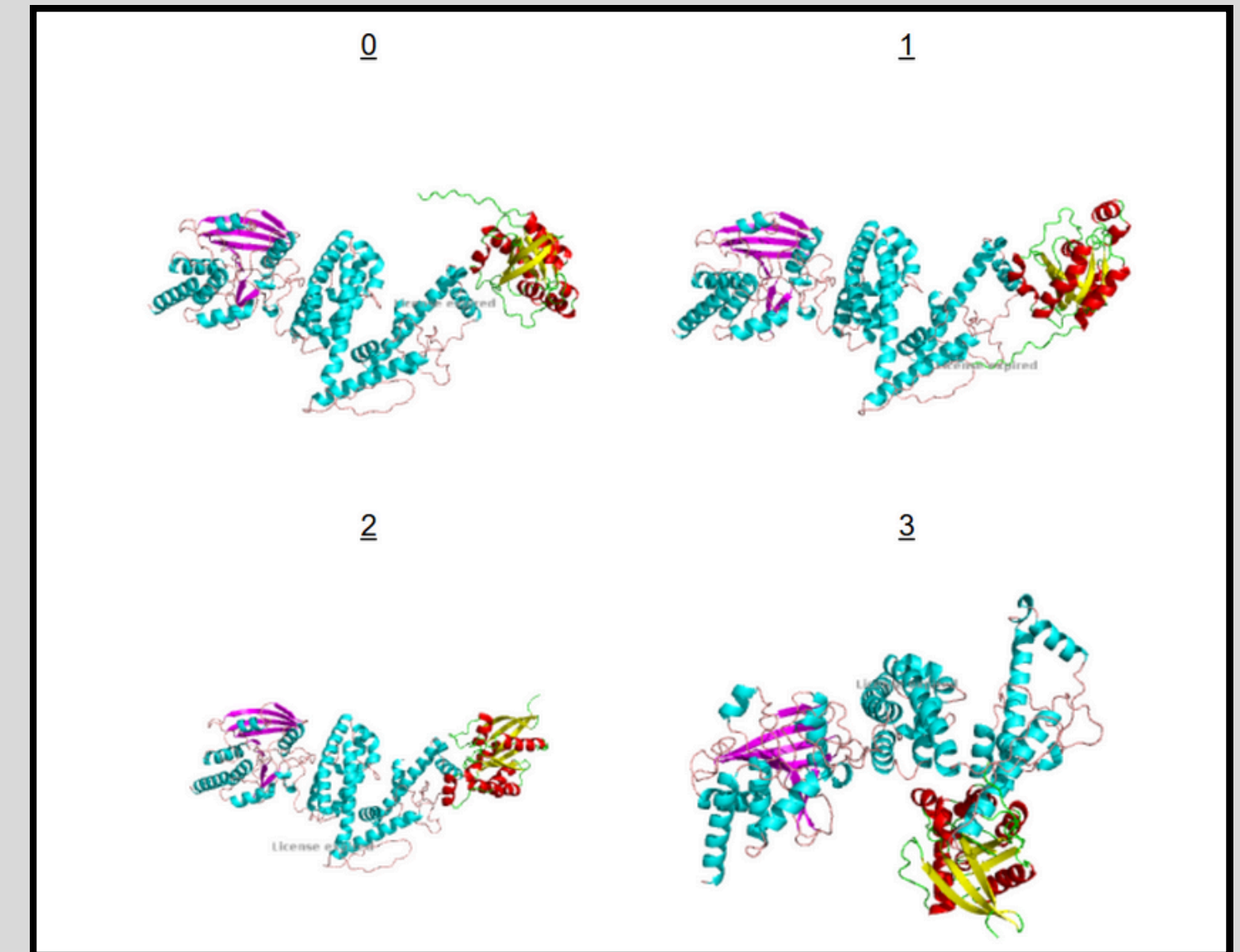
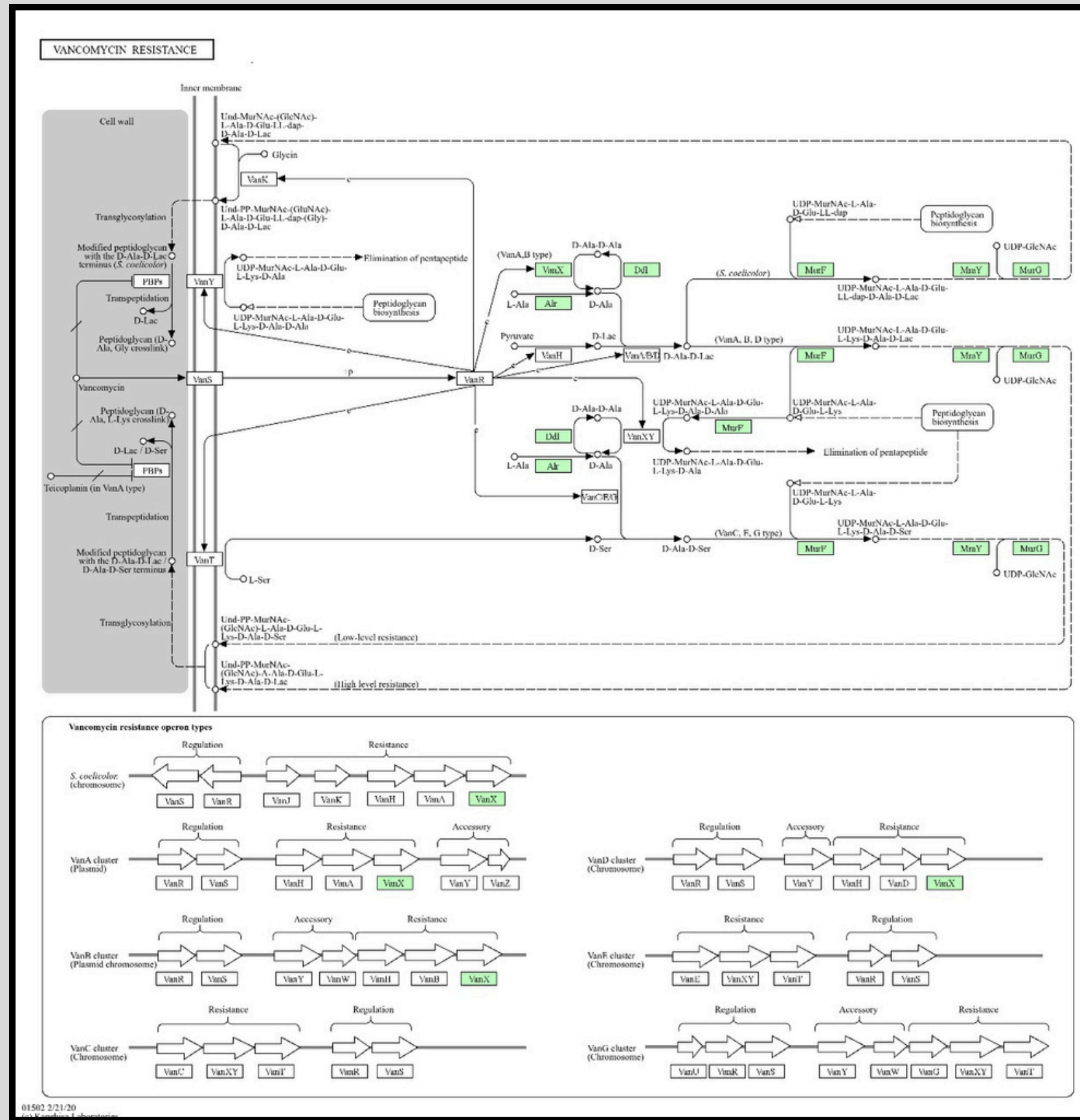


Fig. Output from ClusPro for interaction between host-pathogen

Fig. Output from KEGG for protein interaction between host-pathogen

Tools used

NCBI GenBank & RefSeq

<https://www.ncbi.nlm.nih.gov/datasets/>

AlphaFold Protein Structure Database

<https://alphafold.ebi.ac.uk>

CARD (Comprehensive Antibiotic Resistance Database)

<https://card.mcmaster.ca/analyze/rgi>

UniProt Virulence Factors (Virulence Genes/Proteins)

<https://www.uniprot.org/uniprotkb>

KEGG Pathways (bacterial genes interacting with host proteins)

<https://www.genome.jp/kegg/pathway.html>

Ethical Challenges

1. Responsibility & Overuse

- Healthcare Providers – Overprescription due to patient pressure and uncertainty.
- Patients – Self-medication and incomplete antibiotic courses.

2. Public Health vs. Individual Health

- Doctor's Dilemma – Balancing immediate patient needs vs. preventing long-term resistance.
- Moral Responsibility – Ethical use of antibiotics to avoid future health crises.

3. Global Inequality

- Rich Countries: Overuse of antibiotics accelerates resistance.
- Poor & Unregulated Markets: Limited access, substandard or counterfeit drugs worsen AMR.

Intellectual Property Rights (IPR) Issues

1. Profit vs. Public Health

- Pharmaceutical companies prioritize profits over developing truly innovative antibiotics.
- Many focus on narrow-spectrum drugs (easier to patent), worsening AMR.

2. Influence on Prescription Practices

- Aggressive marketing of antibiotics increases overuse.
- Pharma companies fund biased research and promotions, influencing doctors' prescribing habits.

3. Research & Development (R&D) Incentives

- Companies hesitate to invest in new antibiotics due to low profitability.
- Governments should offer grants, tax credits, and funding for innovation.

4. Regulation & Global Collaboration

- Stricter patent policies needed to prevent excessive commercialization.
- Fair licensing and data-sharing agreements for global access to new antibiotics.

Proposed Solutions for IPR Issues

- Proposals suggest offering \$1 billion rewards for new antibiotics that meet urgent needs.
- Multiple global partnerships have been formed to develop new antibiotics and to promote responsible use.
- Governments and organizations have proposed global funds to support antibiotic Research & Development.
- Priority review vouchers allow companies developing new antibiotics to fast-track approval for other drugs or sell the voucher to others.
- Incentives and new policies are formed to encourage research in the field of Antibiotic Resistance in many countries.

Ideas Patented

Computational Modeling and Simulating of Host-Pathogen Interactions (US20050055188A1).

Computational model to predict host pathogen interactions would ease concerns regarding animal testing. In addition, it would be desirable to have such a model to Save hours of research time and costs

Glycomimetics to Inhibit Pathogen-Host Interactions (US9605014B2).

This patent includes computer-aided methods for generating glycomimetics designed to inhibit pathogen-host interactions, highlighting the application of computational tools in therapeutic development.

References

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