Core Antibiotic-Induced Transcriptional Signatures Reflect Susceptibility to All Members of an Antibiotic Class

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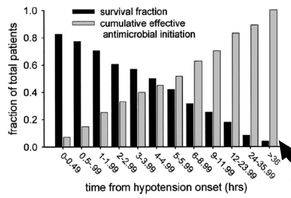
Motivation

Current antibiotic susceptibility testing (AST) is too slow to inform key clinical decisions

- Slow diagnostics cause overuse of empiric antimicrobials
- Every hour counts, but current diagnostic methods take days

[1] **Sepsis mortality increases with every hour of delayed, effective treatment**



Current microbial diagnosis takes 2-3 days for most bacteria

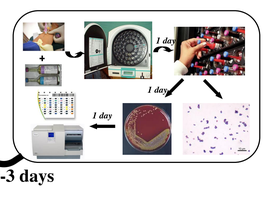


Figure 1

GoPhAST-R provides AST in *hours instead of days*

GoPhAST-R can inform treatment >1 day earlier than current standards

- GoPhAST-R = combined **Geno**typic and **Ph**enotypic **AST** using **R**NA detection

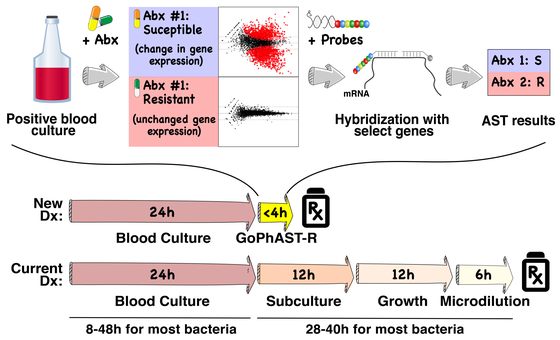


Figure 2

Machine learning identifies top 10 antibiotic-responsive genes that predict susceptibility

[2]

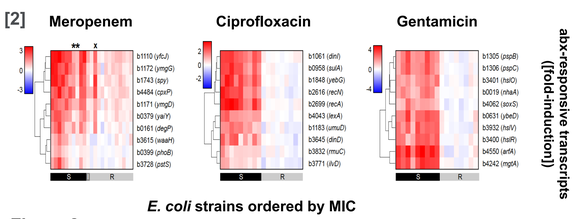


Figure 3

Extending GoPhAST-R to more antibiotics

Can the "top 10 genes" reflect susceptibility for related antibiotics?

- Transcriptional signatures are related to drug mechanism of action
- Clinical benefit: increased flexibility of development and implementation of GoPhAST-R
- Biological interest: understand relation of antibiotic-induced responses within drug classes

For *E. coli* and *K. pneumoniae*:

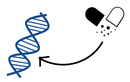
We used the top 10 genes identified for *individual drugs* and analyzed their AST prediction across *other members* of the same class

Individual drug	Antibiotic class
Ciprofloxacin	Fluoroquinolones (DNA gyrase inhibitors)
Gentamicin	Aminoglycosides (30S subunit inhibitors)
Meropenem	Beta-Lactams (Cell wall inhibitors)

Generalizability across fluoroquinolones

Top 10 genes for **ciprofloxacin** predict AST across **fluoroquinolones**

- Mechanism of action: inhibit DNA gyrase



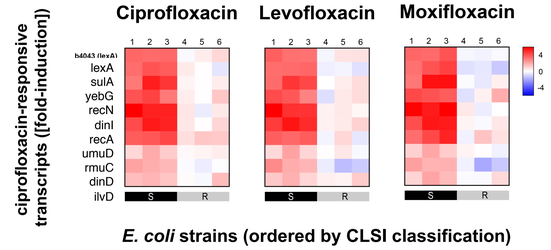


Figure 4

Generalizability across aminoglycosides

Top 10 genes for **gentamicin** predict AST across **aminoglycosides**

- Mechanism of action: inhibit protein synthesis (30S Ribosomal subunit)

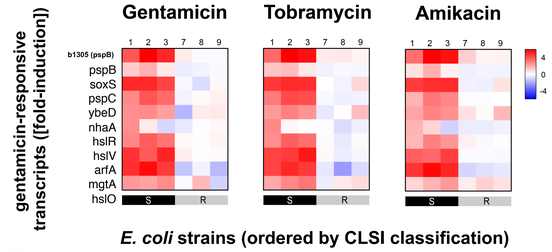
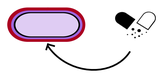


Figure 5

Generalizability across beta-lactams

Top 10 genes for **meropenem** predict AST across **beta-lactams**

- Mechanism of action: inhibit cell wall synthesis



Beta-lactams are a *large* and *diverse* class that span a wide spectrum of activity

- **Rapid AST would allow selection of narrowest effective agent to minimize selection for resistance**

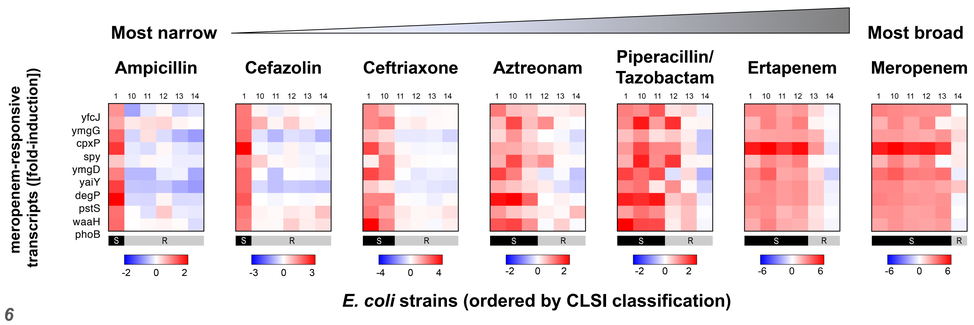


Figure 6

Conclusion

- The top 10 genes identified for AST of **ciprofloxacin**, **gentamicin**, and **meropenem** showed *similar normalized fold-induction* upon treatment with other **fluoroquinolones**, **aminoglycosides**, and **beta-lactams**
- Consistent with a core transcriptional response related to mechanism of action
- These findings will streamline GoPhAST-R implementation, facilitating efficient use of antibiotics

Future work

Test GoPhAST-R performance for GNRs on positive blood cultures in real time

- Collaboration with Massachusetts General Hospital Clinical Microbiology Laboratory
- Compare GoPhAST-R susceptibility calls to gold standard results

Analyze susceptibility signatures with RNAseq across multiple members of different classes

- Uncover the biology behind the "stress response"
- Which pathways are uniquely affected by each drug class?

Key references

1. Kumar A et al, Crit Care Med 2006;34:1589
2. Bhattacharyya et al, Nat Med 2019;25:1858

GoPhAST-R paper
(reference #2)

Summary of this work