THE PEW CHARITABLE TRUSTS

The Shared Platform for Antibiotic Research and Knowledge (SPARK)

A Collaborative Tool to Spark Innovation in Gram-Negative Antibiotic Discovery

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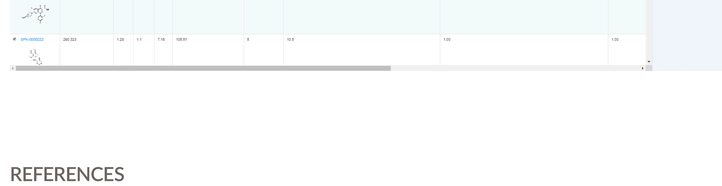
Background

- Significant scientific challenges impede the discovery and development of new antibiotics for Gram-negative pathogens, which are particularly difficult to treat due to their innate efflux and permeation defense mechanisms.
- Economic challenges in antibiotic development force companies to exit this field, risking the loss of valuable research data.
- Sharing results from efforts to answer questions around Gram-negative efflux and permeation is key to advancing the field; a platform that collates "lessons learned" for future research endeavors can minimize costly and time-consuming experimental redundancies.
- SPARK is a free, openly accessible virtual resource that captures and consolidates Gram-negative antibiotic data to assist scientists in the pursuit of novel antibiotics.

To request a SPARK log-in, please visit pewtrusts.org/spark-antibiotic-discovery.

Datasets Are Acquired From All Sectors

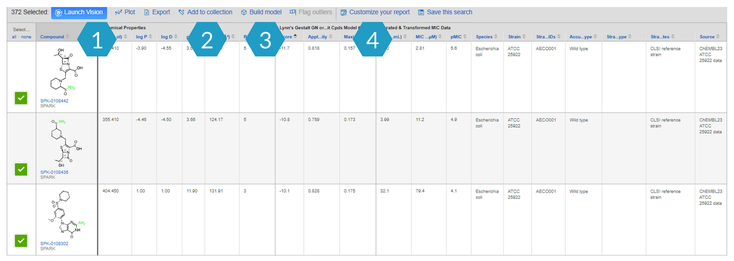
- The SPARK team receives published and unpublished datasets from industry, academic, governmental, and nonprofit sources.
- A global community of antibiotic discovery scientists recommends additional targets of interest and identifies potential data sources.
- The intellectual property of the original contributor is protected.



Data source	Target	Number of MIC & GIC values	Number of IC_{50} values
Industry contributors	LpxADK	538	165
	LpxC	46,761	536
	GyrAB	8,860	53
	Efflux panel	3,498	-
Nonprofit contributors	*Shigella flexneri* XDR *Acinetobacter baumannii*	In progress	
	Agnostic high-throughput screens	3,762	-
Journals	LpxC	1,053	350
	GyrAB	1,649	588
	β-Lactams & β-lactamase inhibitors	910	27
	Agnostic	571	132
	Miscellaneous	7,989	-

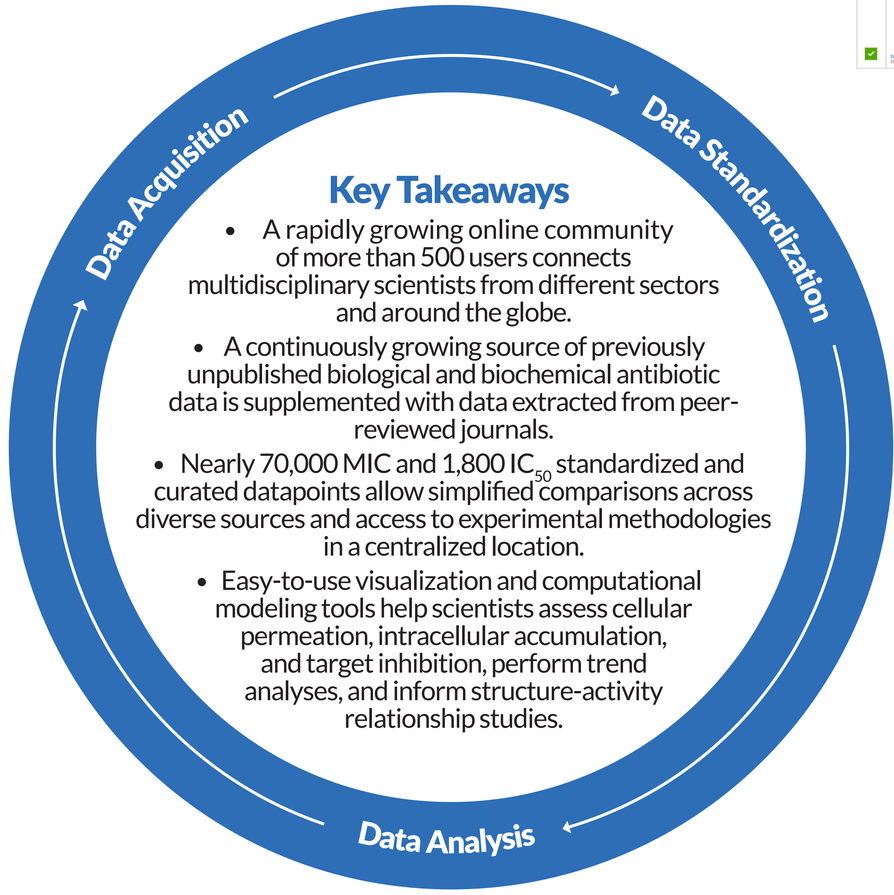
Data Standardization Allows Comparison Across Diverse Sources

- Data scientists transform data from all sources into consistent formats (e.g., µg/mL, µM, nM) for upload into SPARK.
- Experimental conditions, chemical metadata (including structures and physicochemical properties), and strain genotypes and phenotypes are annotated by microbiologist curators.



From the search results screen, you can:

1. Launch the visualization tools to plot results.
2. Create a collection of interesting compounds for easy reference or model building.
3. Build models based on search results.
4. Customize reports.



Key Takeaways

- A rapidly growing online community of more than 500 users connects multidisciplinary scientists from different sectors and around the globe.
- A continuously growing source of previously unpublished biological and biochemical antibiotic data is supplemented with data extracted from peer-reviewed journals.
- Nearly 70,000 MIC and 1,800 IC_{50} standardized and curated datapoints allow simplified comparisons across diverse sources and access to experimental methodologies in a centralized location.
- Easy-to-use visualization and computational modeling tools help scientists assess cellular permeation, intracellular accumulation, and target inhibition, perform trend analyses, and inform structure-activity relationship studies.

SPARK Makes Complex Visualization and Modeling Easy

- Search fully customizable readouts that can be exported for further analysis.
- Create publication-quality scatter plots and histograms.
- Generate predictive models to identify interesting compounds and scaffolds.
- Access on-demand training materials and recorded webinars.

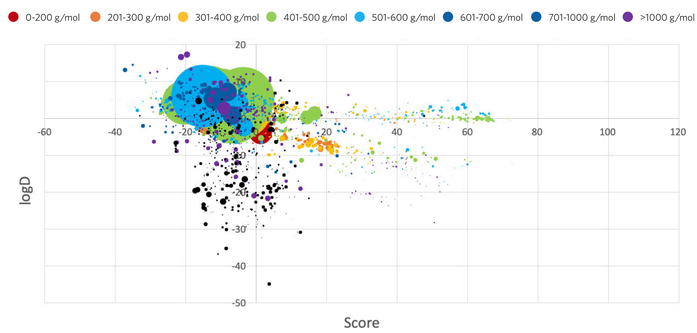
On the left is a predictive model generated in SPARK using a training set of 97 compounds described by Silver (2016) as having Gram-negative activity and tested against ~5000 published compounds and then applied to all curated compounds in SPARK.

The integrated visualization tool can:

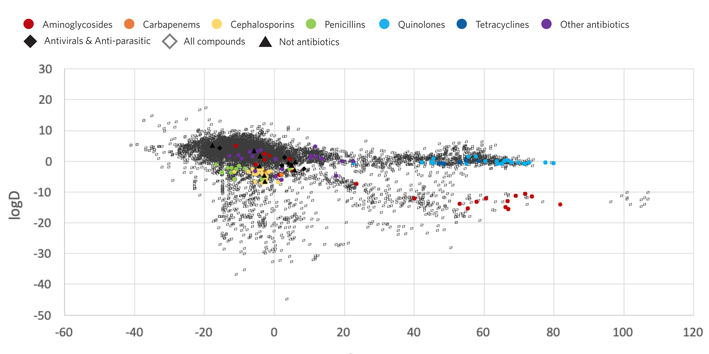
1. Plot outputs of searches and predictive models with up to four parameters on each graph.
2. Filter data points by any parameter from the search readout.
3. Hover over data points for structures (biapenem is highlighted here).

Additional Analysis Can Lead to Further Insights

Data can be exported from SPARK and graphed in Excel. Model scores derived from the integrated tool in SPARK are plotted on the x-axis, and logD is plotted on the y-axis.



Size indicates Escherichia coli *ATCC 25922 MIC and colors represent molecular weight.*



Colors represent drug class.

REFERENCES

[1] Joe Thomas et al., "Shared Platform for Antibiotic Research and Knowledge: A Collaborative Tool to SPARK Antibiotic Discovery," *ACS Infectious Diseases* 4, no. 11 (2018): 1536, https://pubs.acs.org/doi/10.1021/acsinfecdis.8b00193.

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[3] Lynn L. Silver, "A Gestalt Approach to Gram-Negative Entry," *Bioorganic & Medicinal Chemistry* 24, no. 24 (2016): 6379, https://doi.org/10.1016/j.bmc.2016.06.044.

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[5] Michelle F. Richter et al., "Predictive Compound Accumulation Rules Yield a Broad-Spectrum Antibiotic," *Nature* 545, no. 7654 (2017): 299, https://doi.org/10.1038/nature22308.