ArrePath

A new path to combatting AMR through antibiotics with novel MoAs

ArrePath

Executive Summary

Novelty and know-how

ArrePath is integrating machine learning approaches to produce better starting-points for finding antibiotics with novel MoAs

Validated Platform, Pipeline, and Strategy

Our discovery platform already yielded novel broad-spectrum resistance-resistant antibiotic leads with *in vivo* activity

Future plans: develop existing leads and apply the platform to proprietary libraries to ID more novel leads

Leadership

ArrePath is founded by prominent microbiologists and drug hunters with strong track records

Fundraising

ArrePath is raising a Seed Round of $12M led by BIVF

The ArrePath Team

Management & Research

TBD

CEO/CSO

- Experienced person is being identified and engaged
- Candidate has multiple years of antibiotic drug discovery and management experience in Pharma and Biotech
- Candidate also has expertise in the economic and regulatory aspects of the antibiotics industry

Founder & SAB Chair

Zemer Gitai

PhD

- Conklin Distinguished Professor, Department of Molecular Biology, Princeton University
- Leading expert in antibiotics and bacterial biology
- Awards include Beckman Young Investigator Award, NIH New Innovator Award, and NIH Director's Pioneer Award

Lead Investor

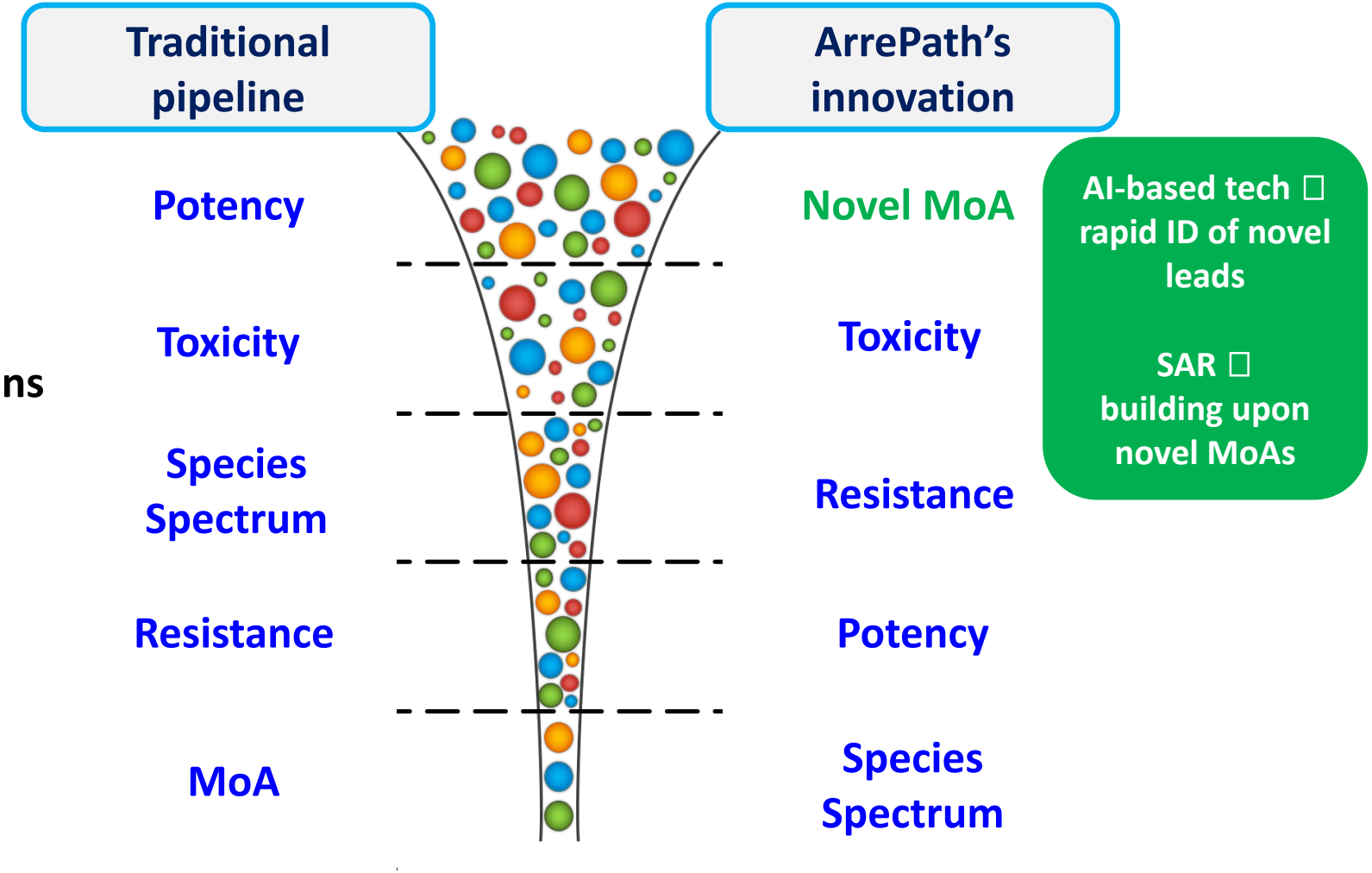
Boehringer Ingelheim Venture Fund

- Strategic venture fund of the Boehringer Ingelheim Corporation, whose strategic focus areas include AMR
- Limited Partner of >$1B AMR Action Fund
- Evergreen fund with €500 under management
- Proven expertise in building and shaping startups and bringing drugs to the clinic
- Boehringer family owned with a strategic long-term vision

We defined a Target Product Profile for the ideal antibiotic and addressed the industry's main bottleneck

Ideal antibiotic TPP

- Broad-spectrum, including Gram-negative bacteria
- Kill existing multi-drug-resistant strains
- Novel mechanism of action
- Not resistance-prone
- Not toxic (effective *in vivo*)



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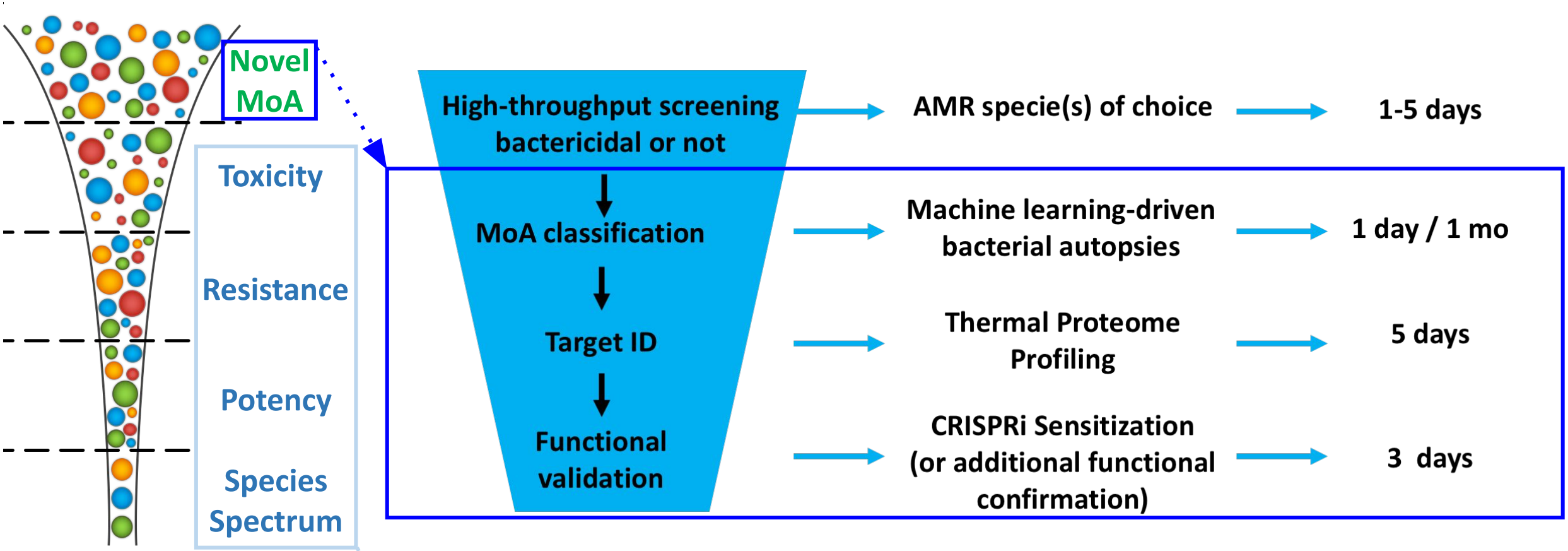
Arrepath's Platform for Rapid Identification of Novel MoA Antibiotics against AMR Pathogens

ArrePath's platform includes innovations to make every step of deconvoluting phenotypic screen hits rapid & quantitative

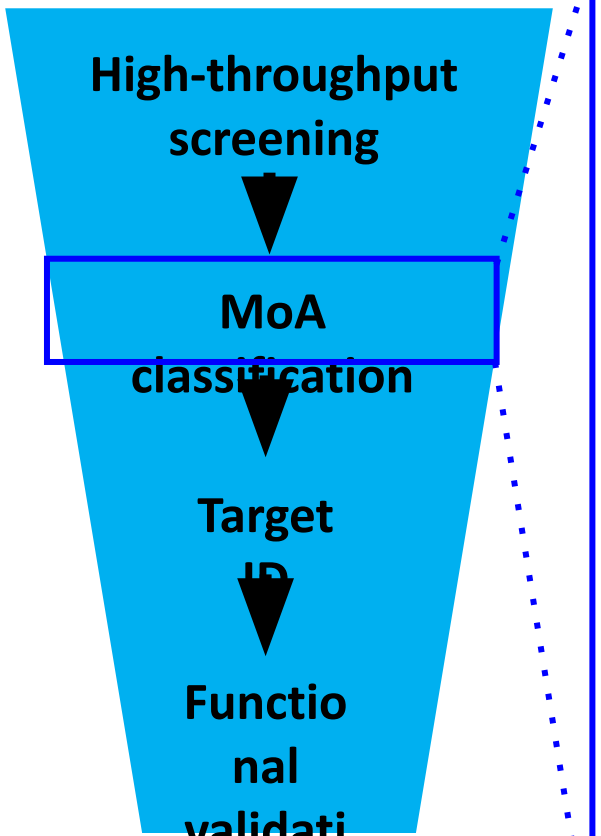
Throughput (based on 32K library)



ArrePath has developed similar innovations for all other pipeline steps

Bacterial autopsies (imaging + ML) enable rapid identification of antibiotics with unique MoAs

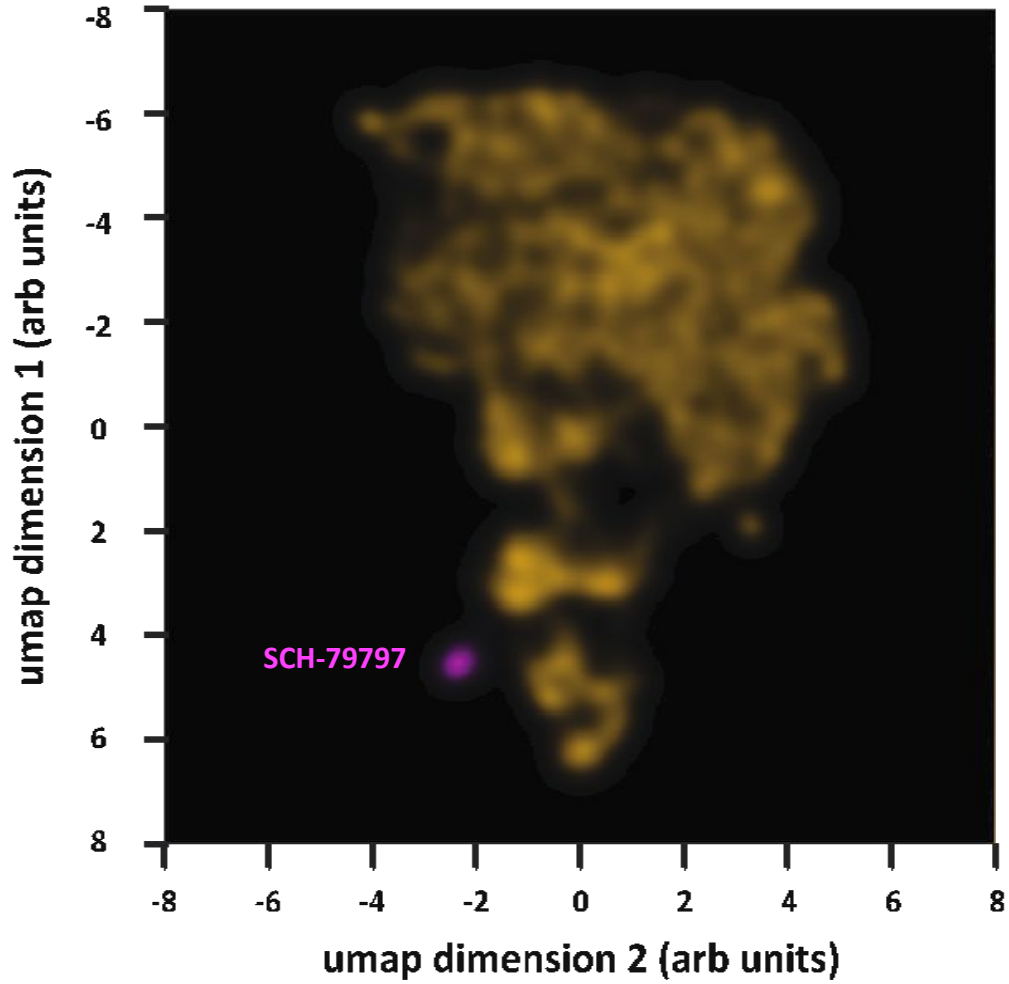
Clustering away from known antibiotics indicates a novel mechanism of action



Instead of measuring growth, we take movies of how the bacteria die

Use computer vision to extract 14 parameters from the movies

Use machine learning to compare the "death trajectories" of our new antibiotics to those of all known antibiotics



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Rapid target ID and functional validation with novel toolboxes

High-throughput screening

MoA classification

Target ID

Functional validation

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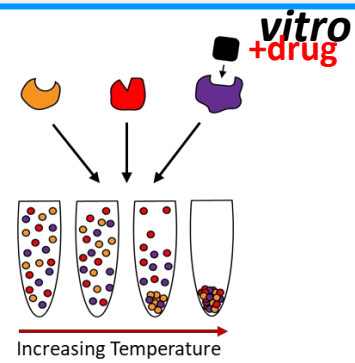
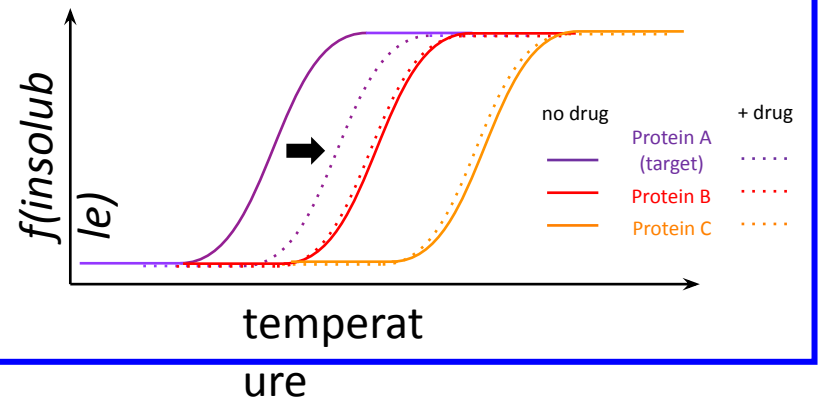
Thermal Proteome Profiling uses Proteomics to identify direct binding targets *in vitro*

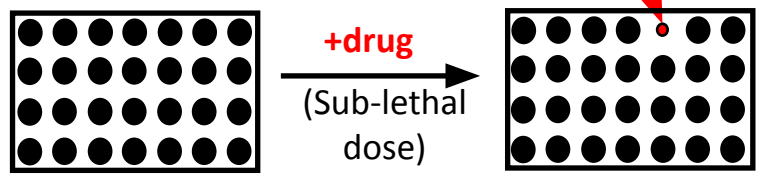
Small molecule binding thermally stabilizes proteins. That thermal shift can be detected by MS.

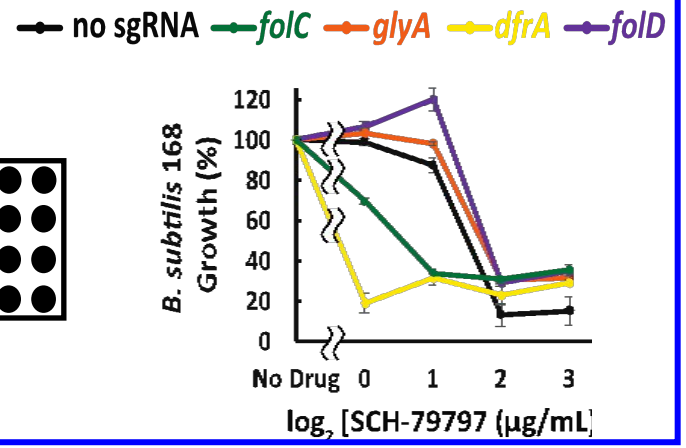




CRISPRi Sensitization validates functional drug-target interactions *in vivo*

CRISPRi Library reduces the levels of each essential gene 3X. Reducing target levels sensitizes bacteria to drug treatment.



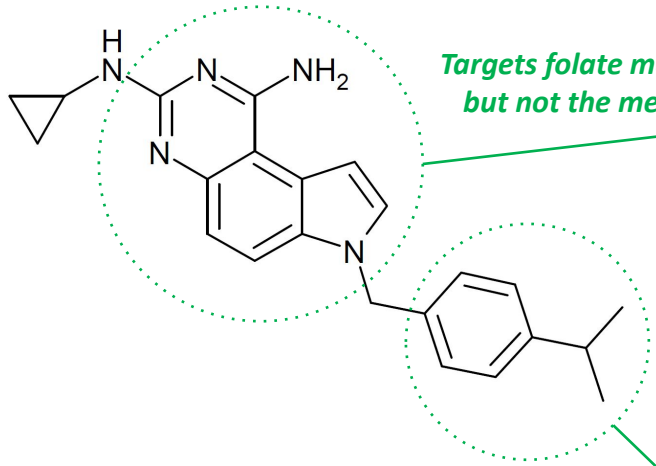


The novel “poison arrow” mechanism of our first hit, SCH-79797, guided SAR to develop our top lead, Irresistin-16

ArrePath’s platform to identify novel MoA hits

SAR based on defined novel MoA (H2L)

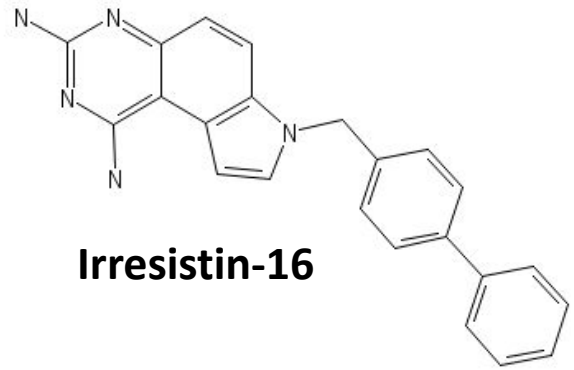
SCH-79797 has 2 functional moieties



Targets folate metabolism but not the membrane

Targets membrane permeability but not folate metabolism

SAR



Irresistin-16

The Poison

- Folates are essential for growth (precursors for DNA, RNA, and protein)
- Unlike other folate-targeting antibiotics, ours are highly resistance-resistant

The Arrow

- Membrane holes kill bacteria
- Unlike most membrane-targeters, ours are selective for bacterial membranes

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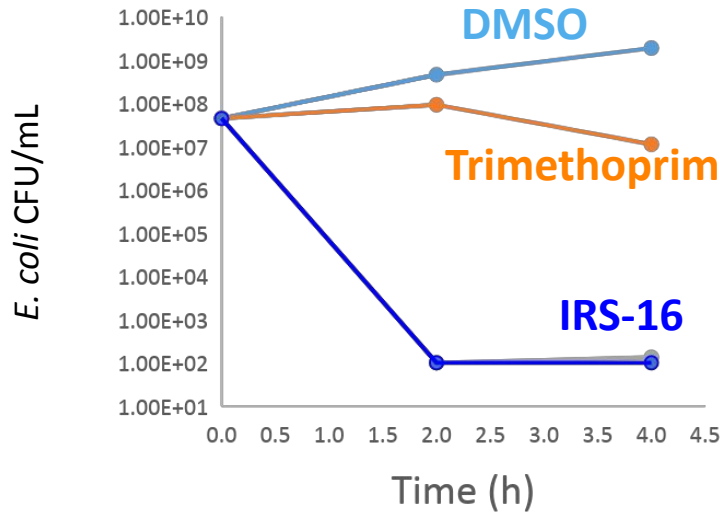
Irresistin-16 quickly kills AMR Gram-positive and Gram-negative pathogens with no detectable resistance

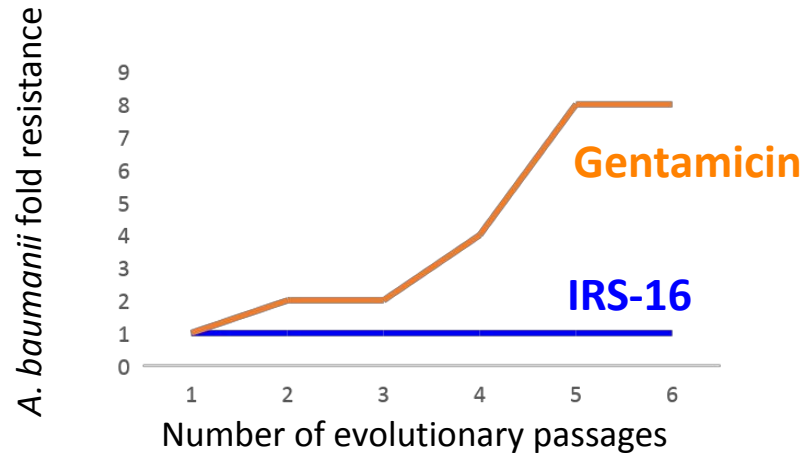
Isolate	MIC (µg/mL)
A. baumannii	3.1
A. baumannii *	3.1
B. subtilis	0.02
E. faecalis	0.016
E. faecium	0.125
E. faecium *	0.125
E. cloacae	0.5
E. coli	0.8
E. coli *	0.8
H. influenzae	4
M. abscessus	3
M. tuberculosis	1.5
M. tuberculosis *	3
N. gonorrhoeae	0.063
N. gonorrhoeae *	0.031
S. typhimurium	4
S. aureus	1.6
S. aureus *	0.5
S. pneumoniae	0.25
V. cholerae	0.4

Gram-positive
Gram-negative
**** MDR strain***

Fast Killing Kinetics



Resistance-resistant



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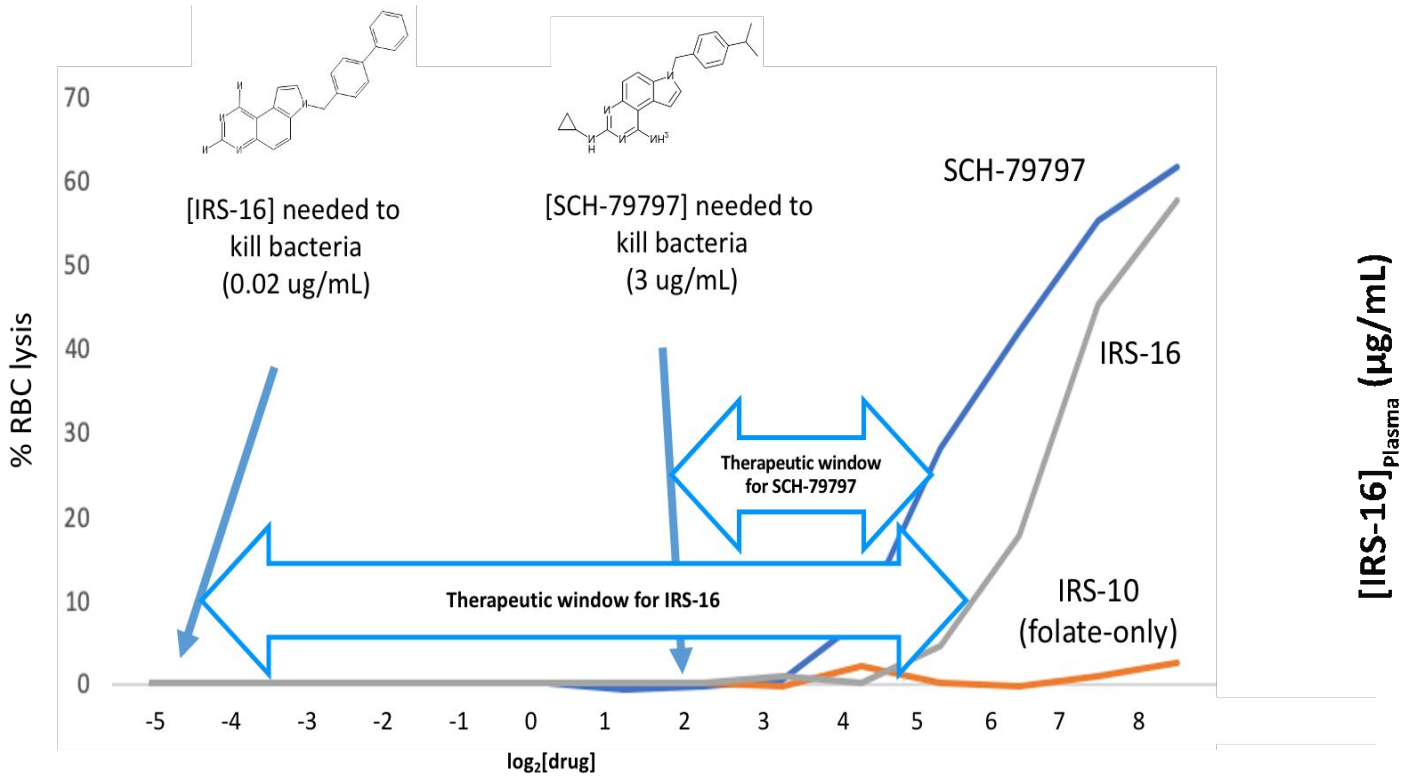
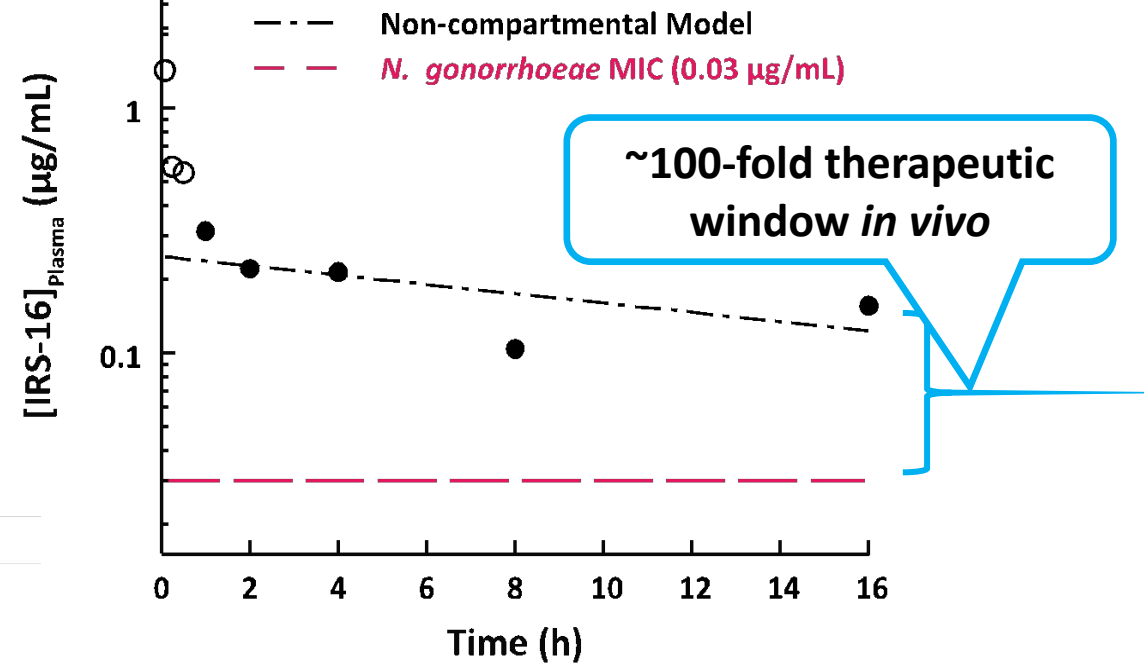
Irresistin-16:
>100-fold Therapeutic Window with desired PK profile



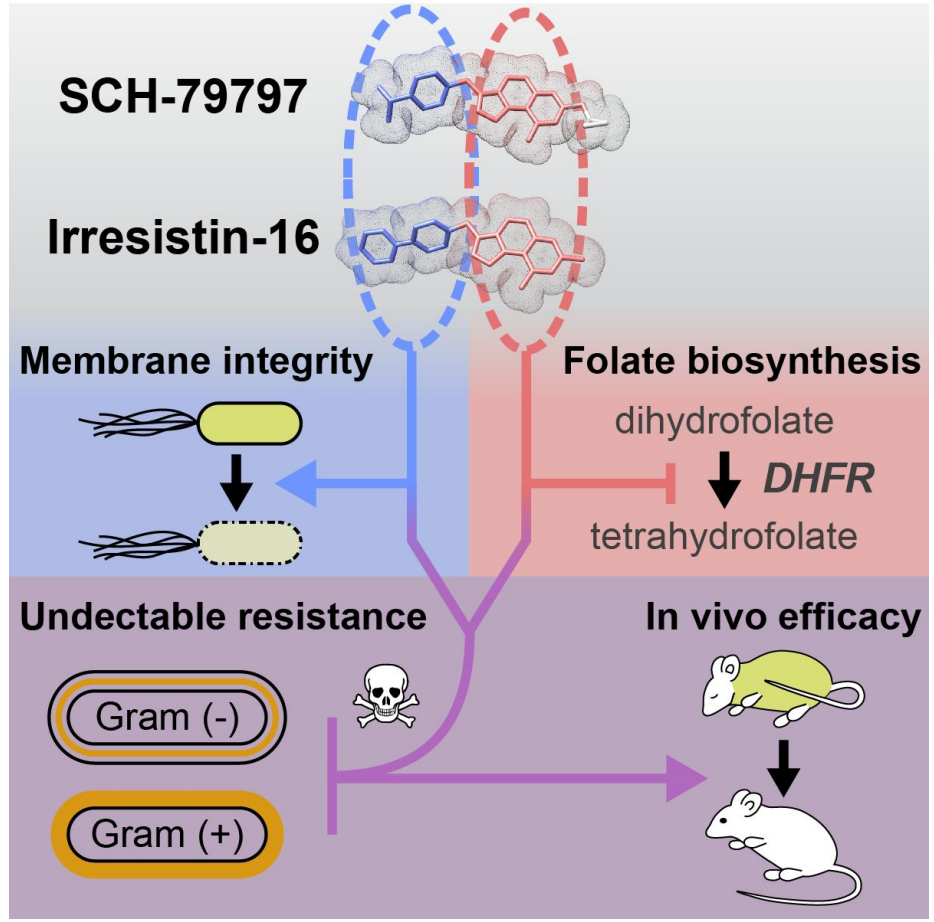
PK values: 15 mg kg^{-1} IV	
$\tau_{1/2}$	15.8 h
AUC (0-16 h)	3.054 h µg mL^{-1}



Have promising preliminary *in vivo* efficacy data in gonorrhoeae mouse model
Seed funding will be used to expand *in vivo* efficacy in multiple infection models

Arrepath's first lead, Irresistin-16 looks like an ideal new antibiotic

- Kill both Gram-positive and Gram-negative bacteria ✓
- Kill existing multi-drug-resistant strains ✓
- Novel Mechanism of Action ✓
- Not resistance-prone ✓
- Not toxic (effective *in vivo*) ✓

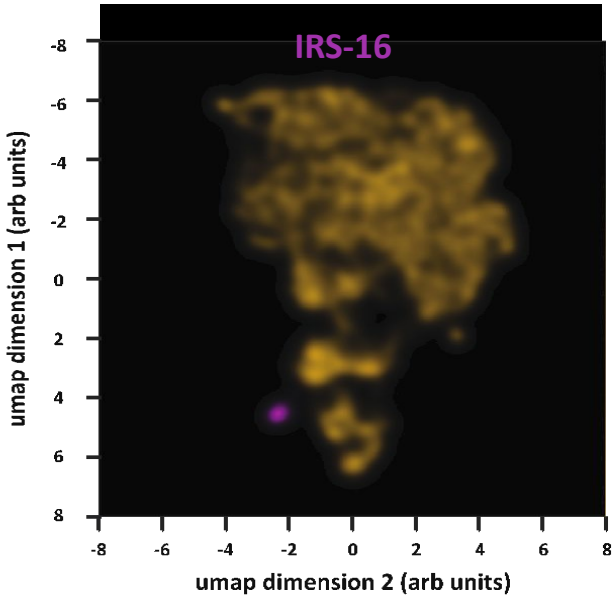


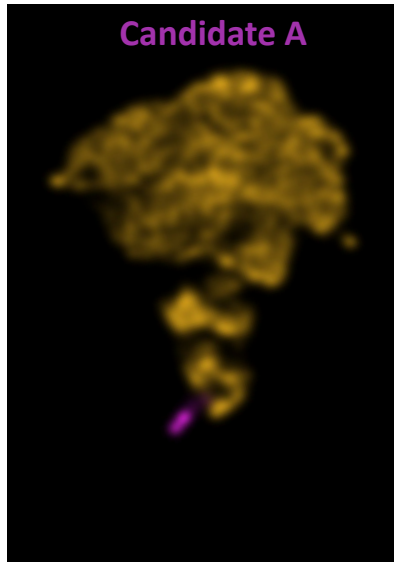
Martin and Gitai et al., *Cell* 2020

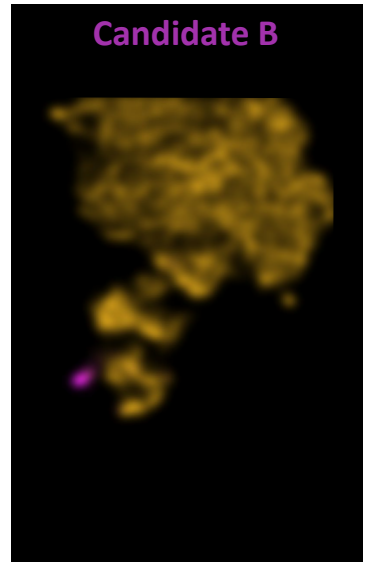
Our pipeline has also yielded a second lead that meets our TPP

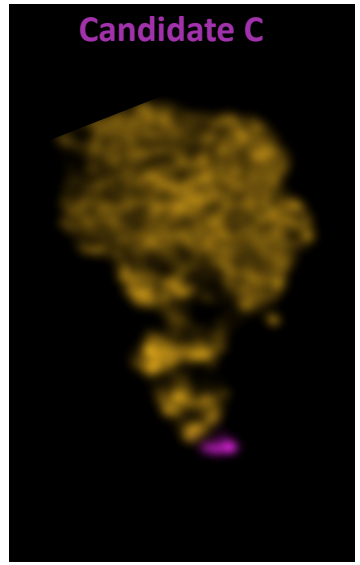
Validating that our platform can identify additional hits

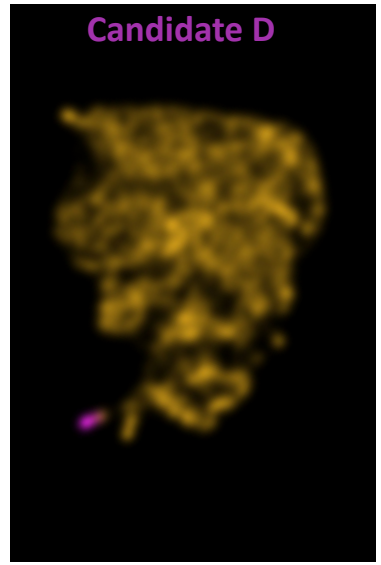
Bacterial autopsies identified additional hits with novel MoAs











Membrane-indepenent?	-	+	-	-	+
Resistance-resistant?	+	+	?	?	+
Target Gram-neg?	-	+	+	+	+
Low toxicity?	+	+	?	?	-

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Proposed business plan priorities

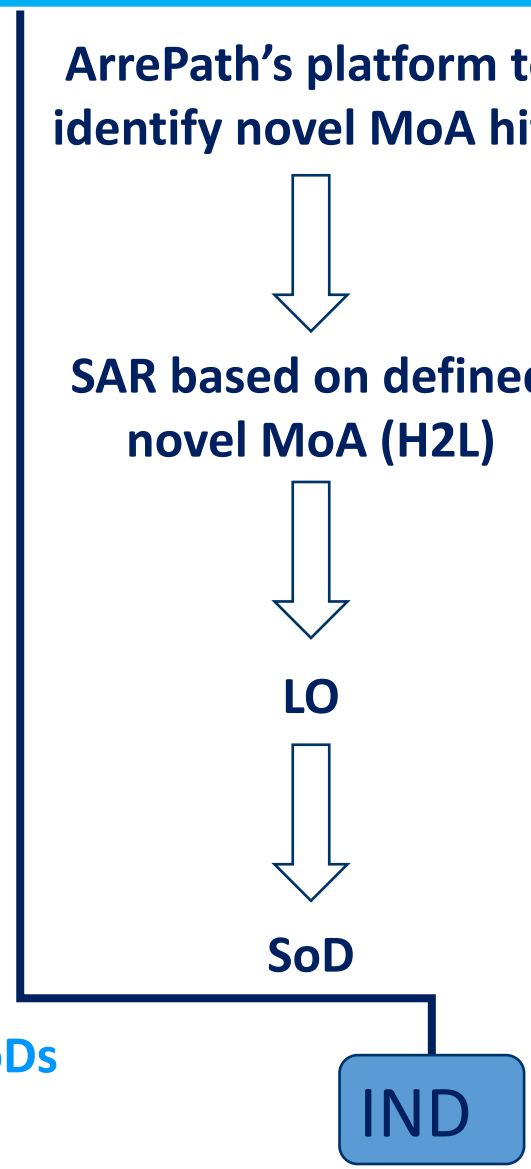
Short-term Goal: Further lead optimization and characterization of Irresistins towards IND

(e.g., *Gram-negative Pneumonias / Gonorrhoea / Tuberculosis**) 15%

Mid-term Goal: Develop additional leads from initial screen or additional libraries w/ existing platform 25%

Long-term Goal: Re-establish the platform with given AMR specie(s) of choice, identify new leads by screening new libraries 60%

(e.g., *Pseudomonas aeruginosa / Klebsiella pneumonia / Acinetobacter baumannii**)



* To be aligned with the BoDs

It’s a big market, but some companies have recently failed. Why will ArrePath succeed?

ArrePath’s key competitive advantages

1

Breakthrough Innovation

Our novel approaches produce better starting-points for finding antibiotics with novel MoAs

2

Promising Initial Lead(s)

Irresistin-16 has a novel MoA, broad spectrum activity against CDC/WHO priority MDR Gram-negative pathogens, low toxicity, and is resistance-resistant.

3

Platform Technology with Multiple shots on goal

Our initial screen identified additional promising leads with novel MoAs

Our machine learning platform can be readily applied to new compound libraries to find more hits with Novel MoAs

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Summary

- **Developing a novel platform to find new antibiotics with novel MOAs.**

Ask

- **Raising $12M in seed funding to develop three programs and expand our platform.**

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