Progressing an antibacterial drug discovery project – an SME perspective

Guest speakers: Alisa Serio & Victoria Savage

Moderator: Daniel Ritz

Host: Victor Kouassi

27 June 2024

GARDP
Global Antibiotic Research & Development Partnership

REVIVE

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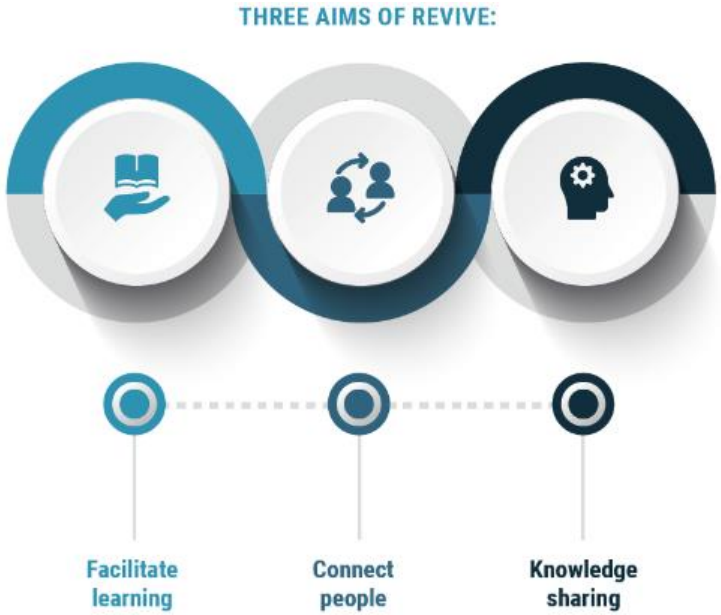

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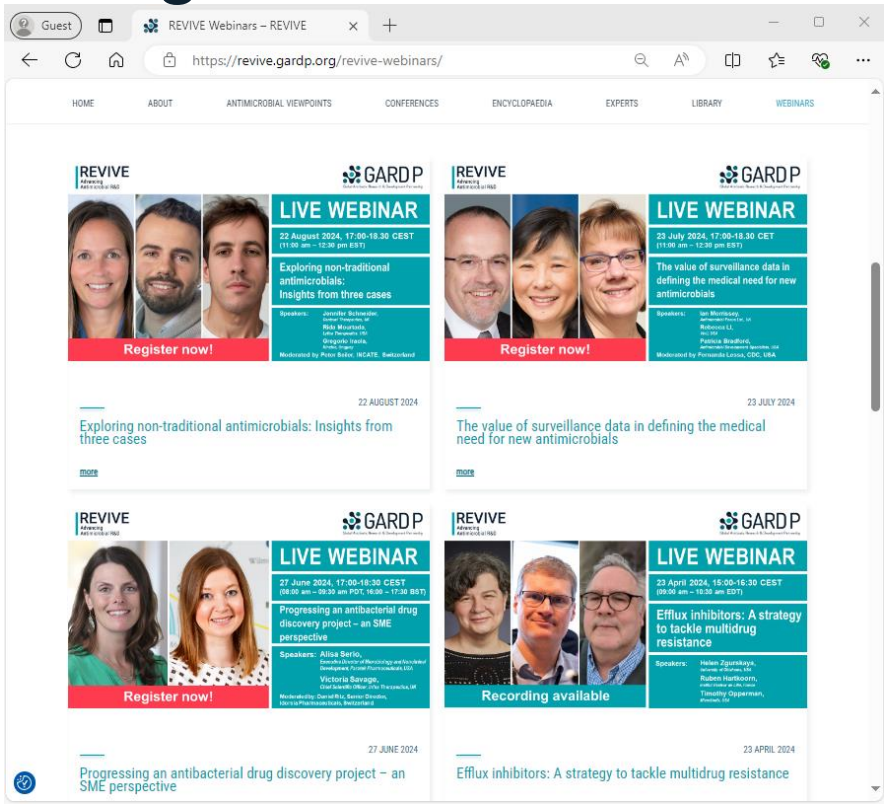

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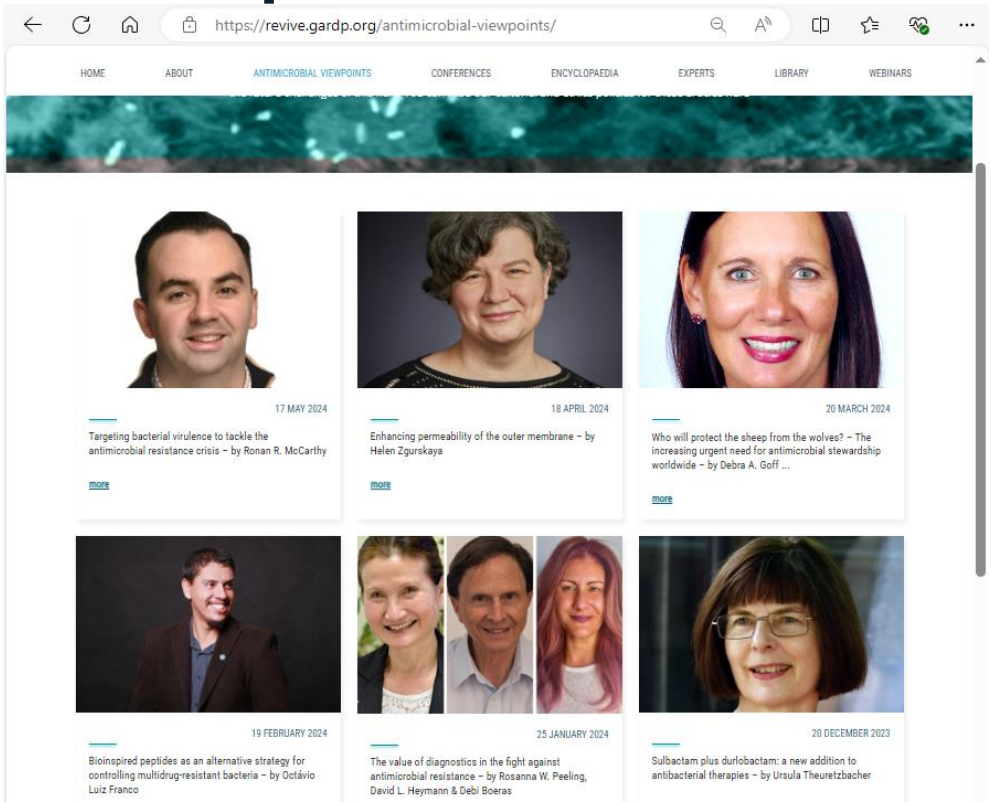
Antimicrobial Viewpoints



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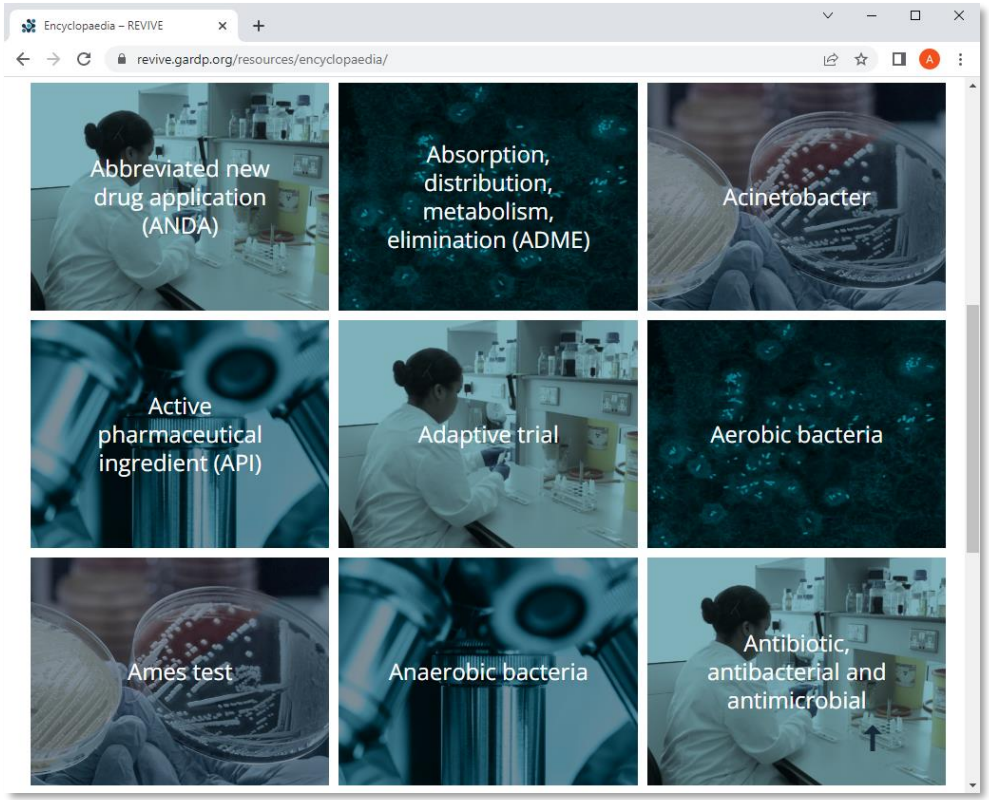
Antimicrobial Encyclopaedia



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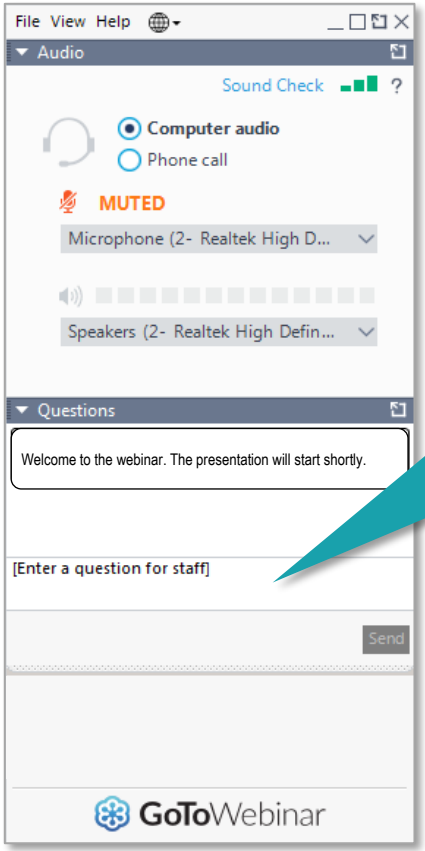
How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

Progressing an antibacterial drug discovery project – an SME perspective

Alisa Serio
Executive Director of Microbiology and Nonclinical Development
Paratek Pharmaceuticals (USA)

Victoria Savage
Chief Scientific Officer
INFEX Therapeutics (UK)

Moderator & Host:
Daniel Ritz
Senior Director – Senior Group Leader
Biology Technologies/ Lead Discovery
Idorsia Pharmaceuticals (Switzerland)

Alisa Serio

Alisa Serio is Executive Director of Microbiology and Nonclinical Development at Paratek Pharmaceuticals, Inc. She has over a decade of experience in antibacterial research and development, in particular in combating antimicrobial resistance (AMR) and has contributed to the FDA approval and commercial launch of new antibiotics as well as research activities under several US government partnerships.

Alisa received her PhD in molecular biology and microbiology from Tufts University Graduate School of Biomedical Sciences, USA and completed a postdoctoral fellowship in molecular and cell biology at the University of California, Berkeley, USA.

Progressing an antibacterial discovery project – an SME Perspective

ALISA W. SERIO, PH.D

EXECUTIVE DIRECTOR OF MICROBIOLOGY AND NONCLINICAL DEVELOPMENT, PARATEK PHARMACEUTICALS INC, USA

Disclaimer

The views and opinions expressed in this program are my own and do not reflect the views or positions of my employer Paratek Pharmaceuticals, Inc

Agenda

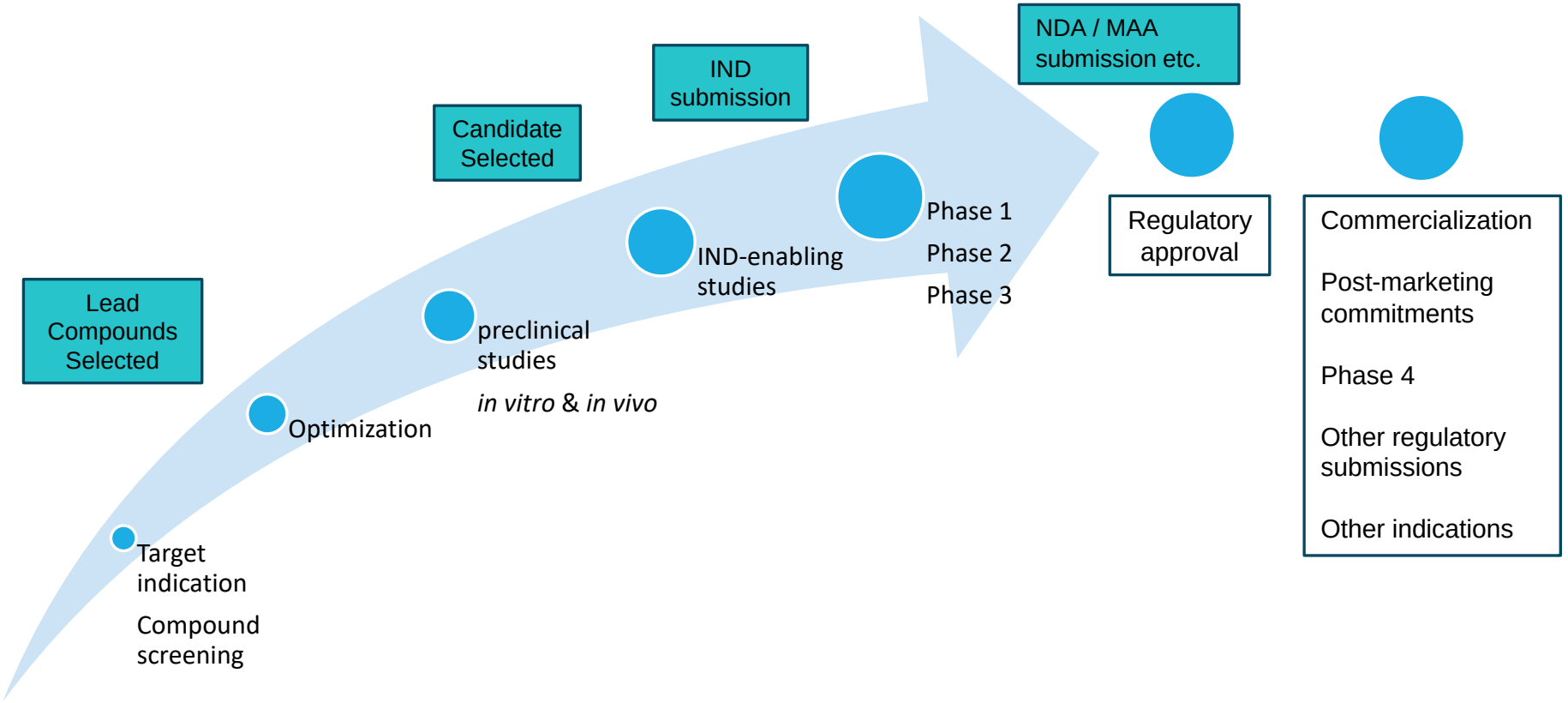
Overview of drug discovery and development process through approval & commercialization

- Key considerations

Examples of Go/No-Go Decisions and Successful Approvals

- Consideration for program origination within SMEs
- Program strategy
- How and when funding can play a role for SME programs

Antibacterial Drug Discovery & Development

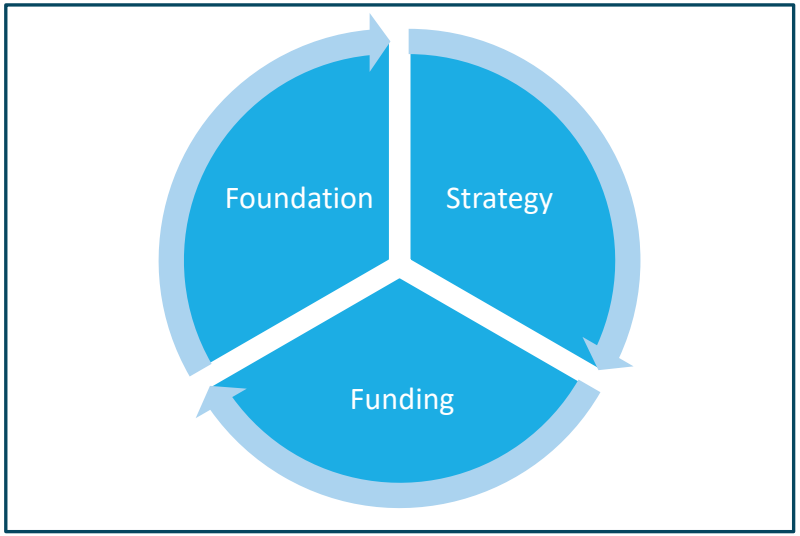


References: 1) The Staggering Cost of Drug Development: A Look at the Numbers – GreenField Chemical Inc.; 2) Financial Innovations Lab – Milken Institute – Models for Financing Antibiotic Development to Address Antimicrobial Resistance

Vignettes

Programs

- Biotin carboxylase
- LpxC inhibitor
- Plazomicin
- Omadacycline



Biotin Carboxylase Inhibitor - Foundation

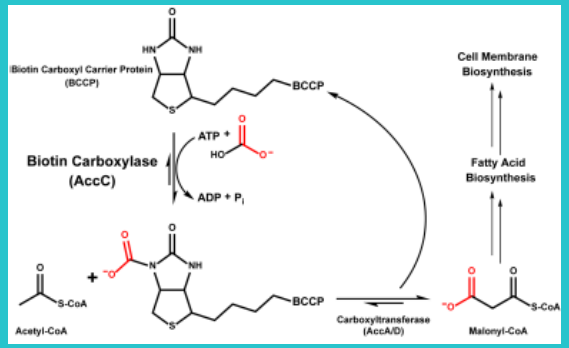
Pfizer[1]

Chemical library screen of 1.6 million eukaryotic-targeted compounds

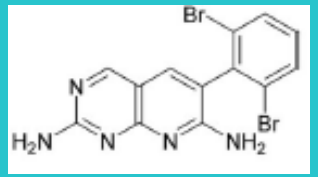
new antibacterial target and compound class

In vitro and in vivo proof-of-concept studies

Biotin Carboxylase Member of Fatty Acid Biosynthesis Pathway[2]



Compound #1[1]



Proof-of-concept Studies[1]

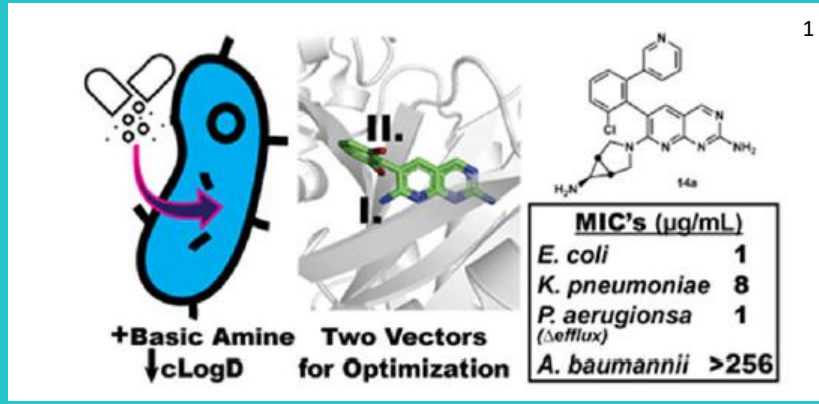
- *in vitro* activity
- BC + #1 in crystal structure
- defined target resistance mutations
- macromolecular synthesis
- bactercidal
- *in vivo* efficacy
- rodent oral & iv PK
- plasma protein binding
- selectivity for bacterial BC vs eukaryotic protein kinases

References: 1) Miller JR et al, Proc. Natl. Acad. Sci. USA 2009, 106, 1737–1742.; 2) Andrews LD et al, J Med Chem. 2019 Aug 22;62(16):7489-7505

Biotin Carboxylase Inhibitor Program - Achaogen

Strategy: Rational optimization using structure guided approach → Funding Opportunity → Optimized physiochemical properties (membrane penetration / efflux) → Improved antibacterial potency

NIH National Institute of Allergy and Infectious Diseases



Reference: 1) Andrews LD et al,. J Med Chem. 2019 Aug 22;62(16):7489-7505.

Biotin Carboxylase Inhibitor Program - Achaogen

Go / No-Go Decision

MIC changes conferred by spontaneous *P. aeruginosa* mutations

	MIC (mg L^{-1})			fold-change from WT		
Strain	1	14a	14e	1	14a	14e
WT background[a]	16	1	8	(1)	(1)	(1)
BC L278F	128	256	64	8	256	8
BC I437N	>128	128	64	>8	128	8
BC I437T	>128	128	64	>8	128	8
MexT F201I	>128	2	8	>8	2	1
MexT P202L	>128	2	8	>8	2	1
MexT V226L	>128	1	8	>8	1	1
INV(*muxA-mexZ*)	>128	32	32	>8	32	4

[a] *P. aeruginosa ΔmexAB-oprM, ΔmexCD-oprJ, ΔmexEF-oprN* [PAM1626 from Ref. 47]

Reference 1

Program Terminated:

Mutants with alarmingly high MIC shifts had either mutations in biotin carboxylase target or efflux pump overexpression[1]

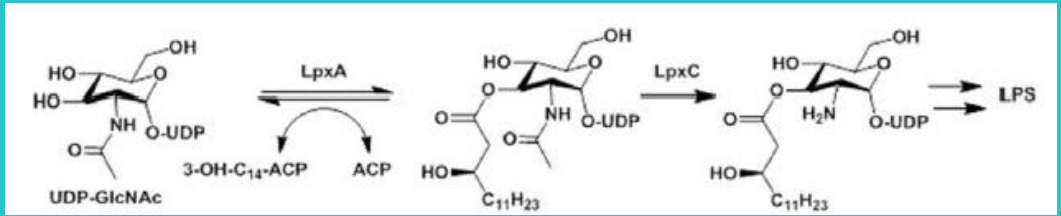
Reference: 1) Andrews LD et al,. J Med Chem. 2019 Aug 22;62(16):7489-7505.

LpxC Inhibitor - Foundation

Novel essential Gram-negative target → Several discovery programs → Inhibitors with antibacterial activity

e.g. Merck (C. Raetz), Chiron, British Biotech, Pfizer etc.[2]

LpxC Catalyzes the First Committed step of LPS Biosynthesis[1]



References : 1) Cohen F et al, ChemMedChem. 2019 Aug 20;14(16):1560-1572.; 2) Erwin A. Cold Spring Harbor Perspectives in Medicine. 2016. doi:10.1101/cshperspect.a025304; 3) Barb AW et al. Curr Pharm Biotechnol 2008 Feb 9(1):9-15

LpxC Inhibitor Program 1 - Achaogen

Strategy:
Medicinal chemistry

→ Funding Opportunities

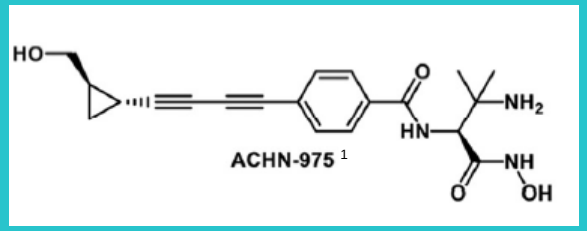
→ Robust Preclinical Program

→ IND

NIH National Institute of Allergy and Infectious Diseases

wellcome

CARB-X
Combating Antibiotic Resistant Bacteria



ACHN-975 [1]

P. aeruginosa (N=250) [1]
MIC_{50} 0.06 µg/mL; MIC_{90} 0.25 µg/mL
Range ≤0.008 to 2 µg/mL

References: 1) Krause KM et al, Antimicrob Agents Chemother. 2019 Oct 22;63(11); 2) Cohen F et al, ChemMedChem. 2019 Aug 20;14(16):1560-1572

LpxC Inhibitor Program 1 - Achaogen

Phase 1[3]
ACHN-975: First-in-Human single ascending dose study

Therapeutic Window:
Can a dose regimen be achieved to reduce potential for resistance / minimize toxicity? [1]

References : 1) Cohen F, et al. ChemMedChem. 2019 Aug 20;14(16):1560-1572.; 2) Erwin A. Cold Spring Harbor Perspectives in Medicine. 2016. doi:10.1101/cshperspect.a025304; 3) https://clinicaltrials.gov/study/NCT01870245

LpxC Inhibitor Program 1 - Achaogen

Go / No-Go Decision #1

Phase 1 Study Terminated

- **Inflammation at the injection site[1]**
- **Cmax-driven dose-limiting toxicity of transient hypotension without tachycardia[2]**

Next Steps

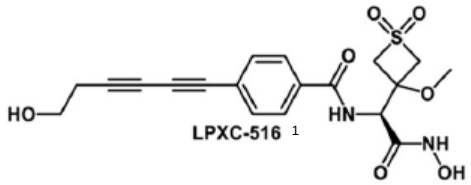
References: 1) Erwin A. Cold Spring Harbor Perspectives in Medicine. 2016. doi:10.1101/cshperspect.a025304; 2) Cohen F, et al. ChemMedChem. 2019 Aug 20;14(16):1560-1572.; 3) https://clinicaltrials.gov/study/NCT01870245

LpxC Inhibitor Program 2 - Achaogen

Focused medicinal chemistry → Alternative leads identified → *In vitro* *In vivo*

Objective

Clinical candidate with wider therapeutic window for cardiovascular safety



- Enzyme potency
- Antibacterial activity
- Resistance
- PK
- Therapeutic window in a rat CV safety assay

DTRA, NIAID, Wellcome, CARB-X

References: 1) Krause KM et al, Antimicrob Agents Chemother. 2019 Oct 22;63(11); 2) Erwin A. Cold Spring Harbor Perspectives in Medicine. 2016. doi:10.1101/cshperspect.a025304; 3) Cohen F et al, ChemMedChem. 2019 Aug 20;14(16):1560-1572; 4) https://clinicaltrials.gov/study/NCT01870245

LpxC Inhibitor Program 2 - Achaogen

Go / No-Go Decision #2

Program Terminated

- **Could not identify optimized clinical candidate with acceptable therapeutic window[1]**
- **Resistance development and magnitude of minimum inhibitory concentration changes could not be covered[2]**

References:
1) Cohen F, et al. ChemMedChem. 2019 Aug 20;14(16):1560-1572.; 2) Krause KM et al, Antimicrob Agents Chemother. 2019 Oct 22;63(11);

Vignettes

Programs

- Biotin carboxylase
- LpxC inhibitor
- Plazomicin
- Omadacycline

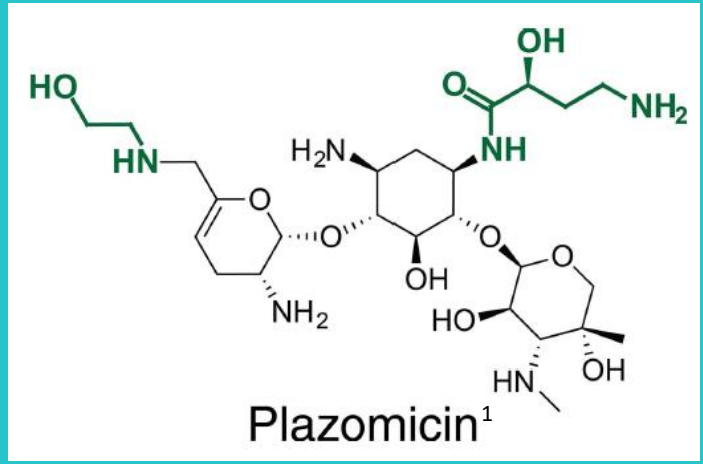
Plazomicin Program Foundation & Strategy - Achaogen

Existing class with extensive history **aminoglycosides**

Strategic medicinal chemistry

- Evade known resistance mechanisms
- Expand spectrum

Hydroxy-Ethyl Blocks AMEs



Plazomicin[1]

HABA group Blocks AMEs

HABA=hydroxy-aminobutyric acid
AME=aminoglycoside modifying enzyme

Reference: 1) Serio AW, et al. EcoSal Plus 2018 Nov;8(1); 2) Aggen JB, et al. Antimicrob Agents Chemother. 2010 Nov;54(11):4636-42.

Plazomicin Program - Achaogen

IND
Phase 1
Phase 2

→

Phase 3
cUTI /AP[1]
BSI due to CRE[2]

→

FDA Approval 2018
cUTI *ONLY*
ZEMDRI™

FDA Breakthrough Therapy Designation (first antibiotic)
FDA Fast Track Designation

NASDAQ

First contract awarded from BARDA's Antibacterials Program[3]

Acquisition of Plazomicin (ZEMDRI™) Approval in India 2024

Reference: 1) Wagenlehner FME et al; N Engl J Med. 2019 Feb 21;380(8):729-740; 2) McKinnell JA et al, N Engl J Med. 2019. Feb 21;380(8):791-793.
3) https://medicalcountermeasures.gov/barda/fdaapprovals/

Omadacycline Program Foundation & Strategy - Paratek

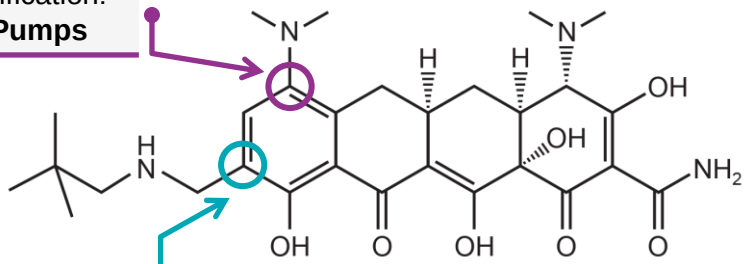
Existing class with long history of safety and utility

tetracylines

Strategic medicinal chemistry

- Evade known resistance mechanisms
- Improve on tolerability (tox/emesis)
- Oral bioavailability

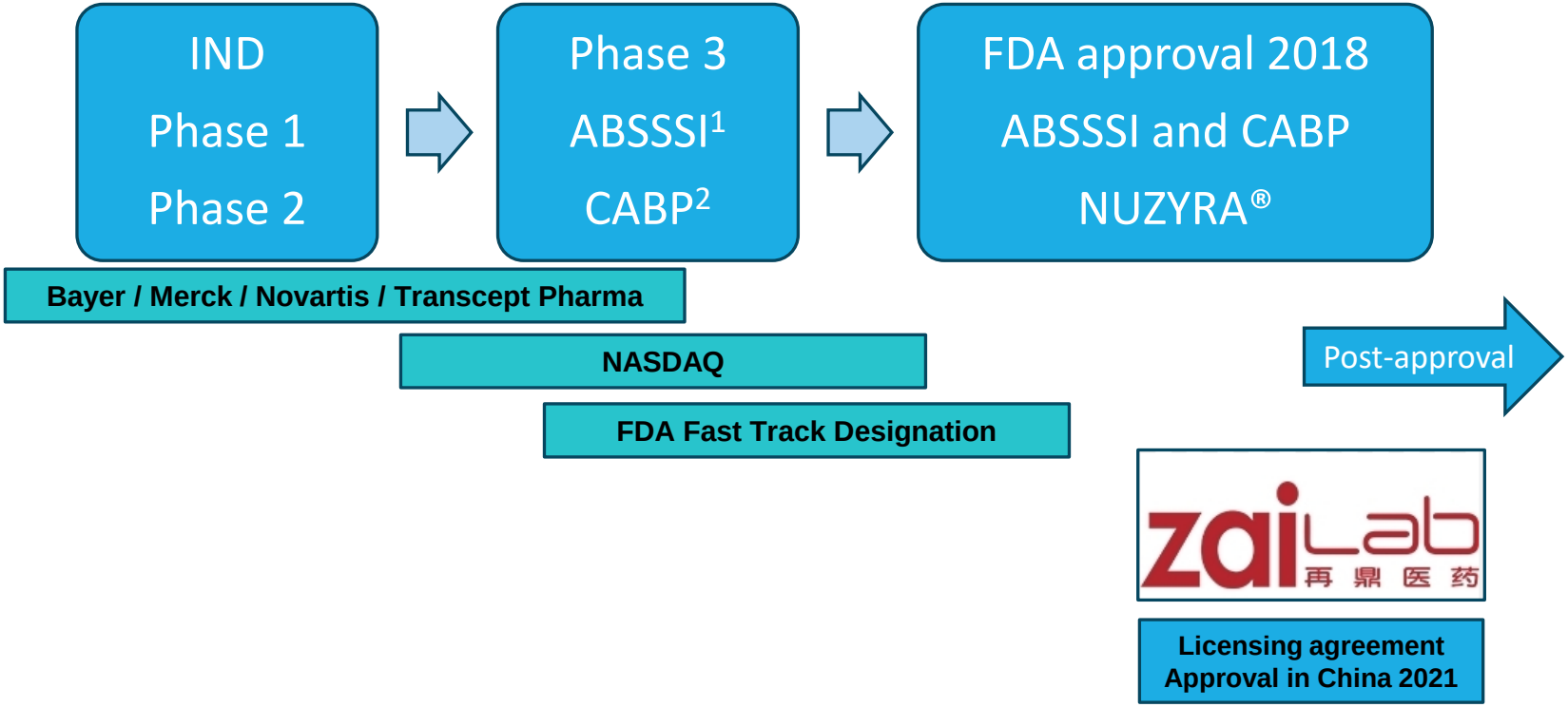
C7-position modification:
Active Efflux Pumps



C9-position modification:
Ribosomal Protection

Reference: 1)Honeyman L et al, Antimicrob Agents Chemother 2015 Nov; 59(11); 2) Macone AB et al, Antimicrob Agents Chemother 2014;58(2):1127-35; 3) Draper MP et al, Antimicrob Agents Chemother 2014;58(3):1279-83

Omadacycline Program - Paratek



Reference: 1)O'Riordan W et al, Lancet Infect Dis 2019 Oct;19(10):1080-1090; 2) Torres A et al; Int J Infect Dis 2021; Mar 104:501; 3) Zhanel G. et al, Drugs 2020; Feb;80(3):285-313

Omadacycline Program - Paratek

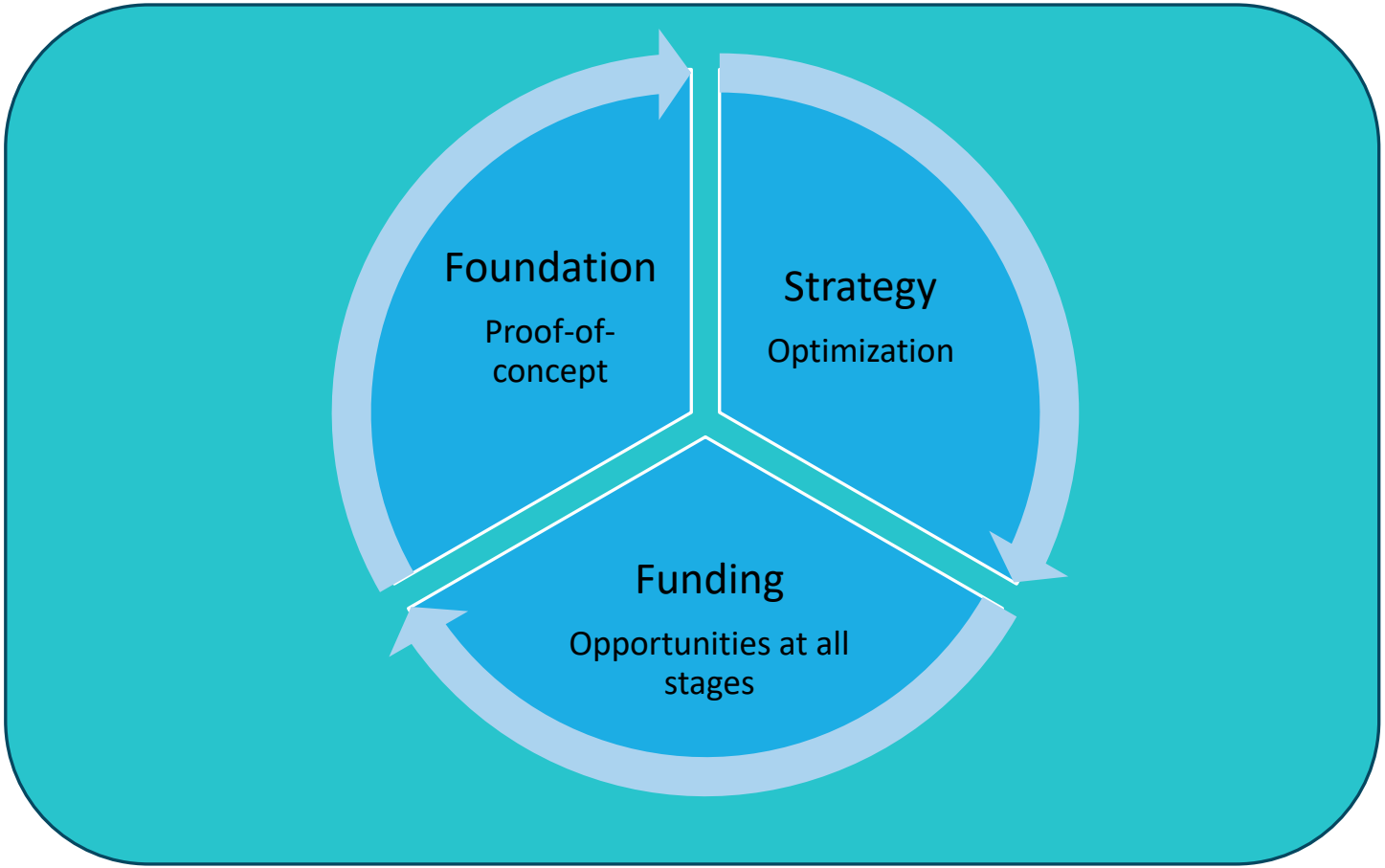
Post-approval → Post-marketing studies → - Required - Development for new indications

Development Programs for New Indications

Treatment and post-exposure prophylaxis of pulmonary anthrax
BARDA Project Bioshield

Non-tuberculous Mycobacteria pulmonary disease[1]
FDA Orphan Designation
EMA Positive Opinion Orphan Medicinal Product

Reference: 1) https://clinicaltrials.gov/study/NCT04922554


Foundation
Proof-of-concept
Strategy
Optimization
Funding
Opportunities at all stages

Thank you

Victoria Savage

Victoria Savage is Chief Scientific Officer of INFEX Therapeutics Ltd, an infection-focused biotechnology company developing several new therapies for drug-resistant infections based in Cheshire, UK.

She is a microbiologist with a keen interest in antimicrobial research and development and has contributed to the development of multiple antimicrobial programs, from early-stage assets through to clinical-stage projects. Victoria has experience in the development of diverse modalities including small molecules, biologics and non-traditional approaches. She gained her PhD in Microbiology and Immunology from the University of Leeds, UK and also serves on several scientific advisory committees in biological sciences.

INFEX THERAPEUTICS

Progressing an antibacterial discovery program – an SME perspective

Dr Victoria Savage
Chief Scientific Officer, Infex Therapeutics Ltd

AMR – The Broken Market

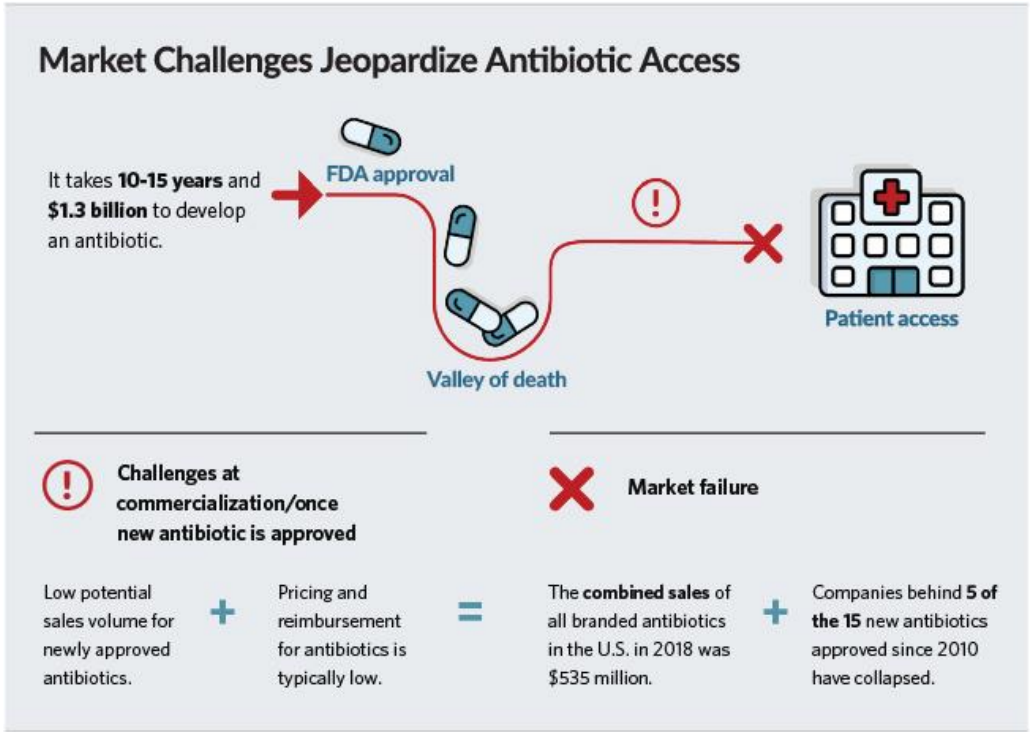


Image: Pew Charitable Trusts

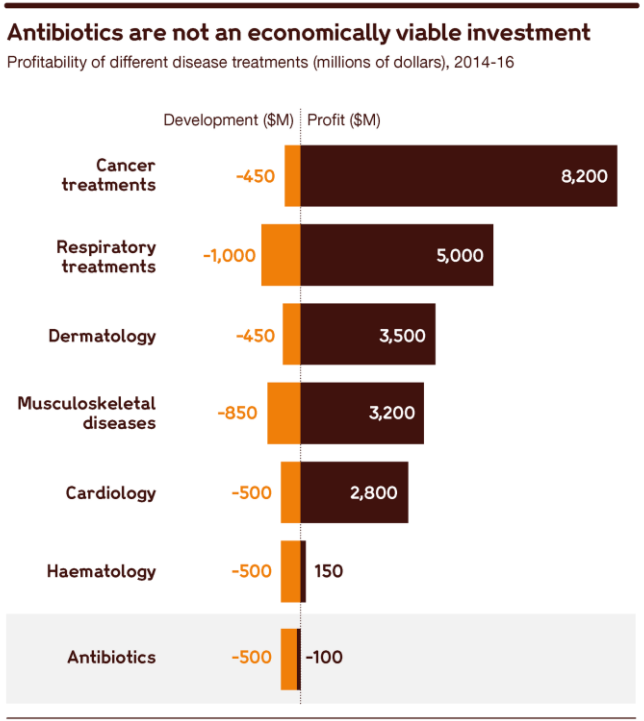
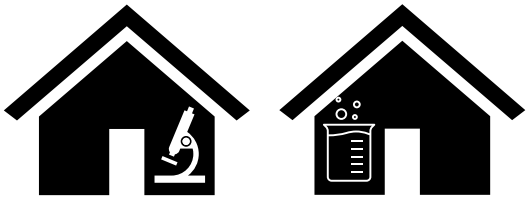


Image: Wellcome Trust

https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2021/antibiotic-development-needs-economic-incentives

https://wellcome.org/news/its-time-fix-antibiotic-market

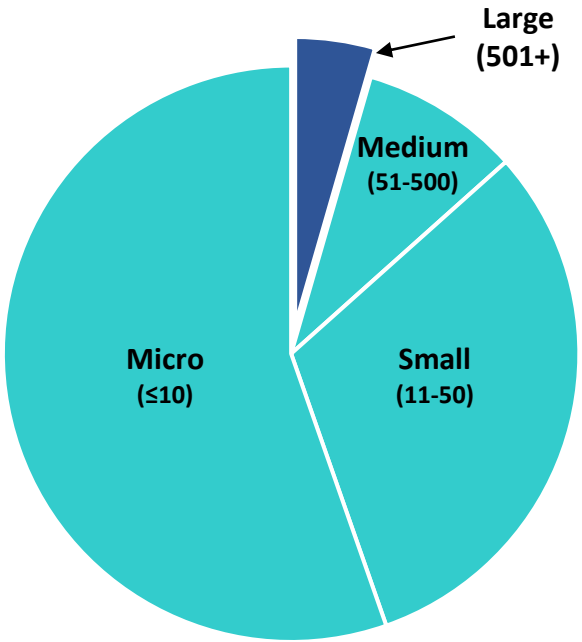
The Role of SMEs in AMR Innovation



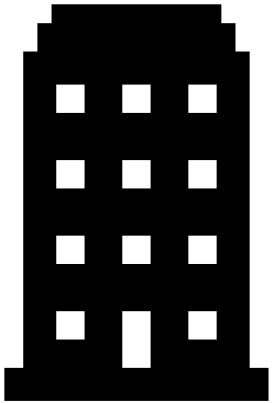
>95% of AMR preclinical pipeline projects are in SMEs

SME: Small to Medium Enterprise

Companies with preclinical pipeline projects by size (employees)



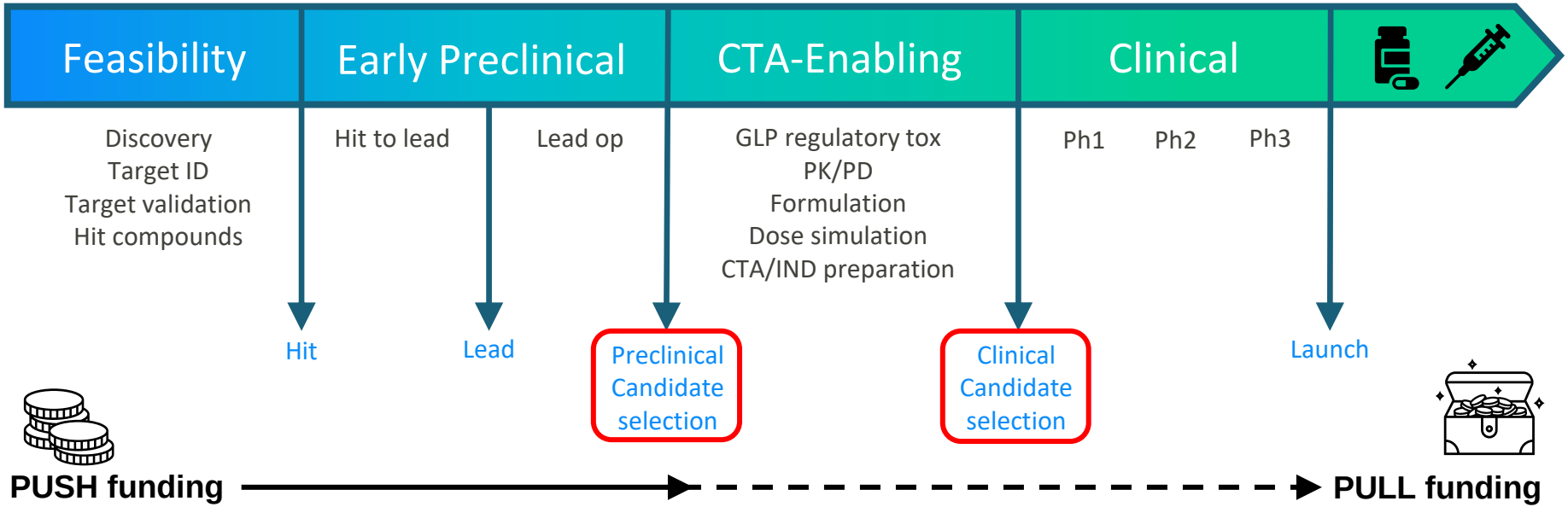
Less than 5% of preclinical AMR innovation occurs in large commercial organisations



World Health Organisation - 2023 Antibacterial agents in clinical and preclinical development

Where SMEs fit in the pipeline

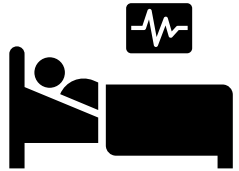
Academia | **SMEs, Pharma, Non-profits** | **Pharma, Non-profits**



Developing new antibiotics

Idea

Development timeline



Clinical need

Target candidate profile (TCP)

Target product profile (TPP)

Product

Go/No-Go Criteria

Assay cascade/funnel

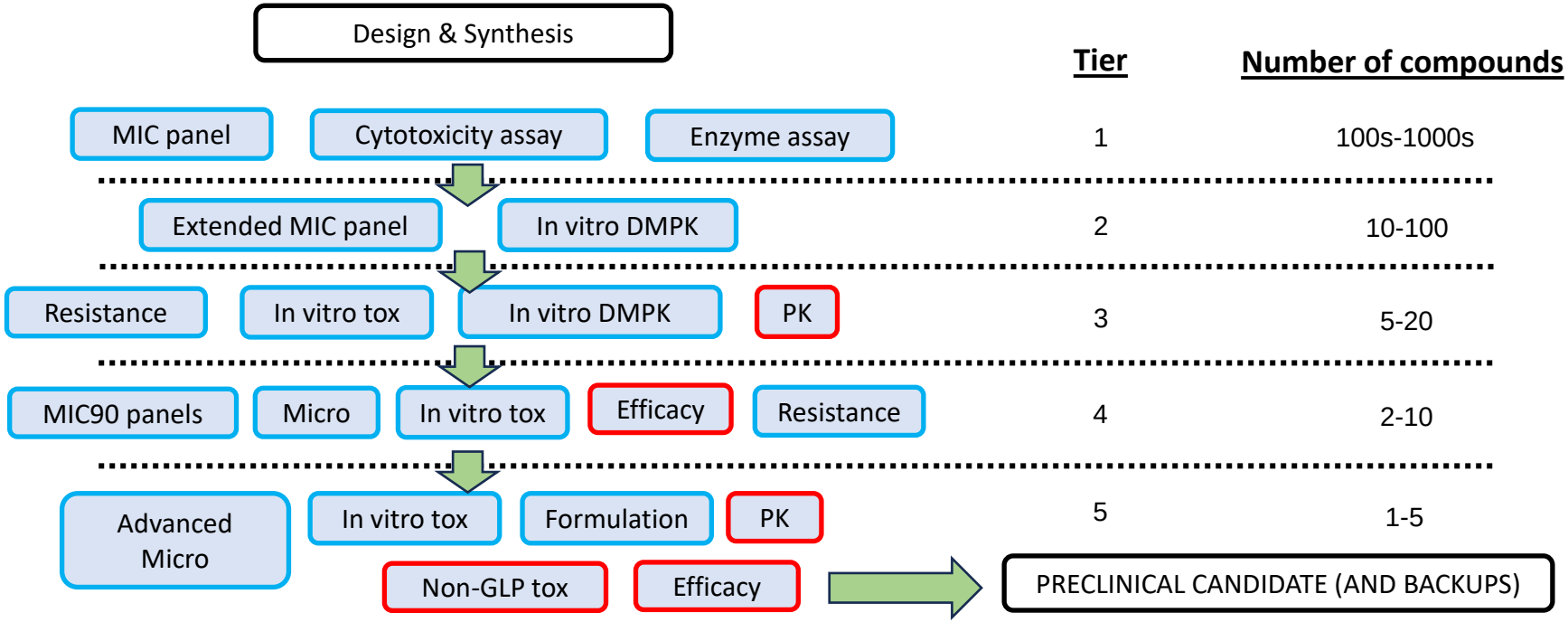
TPP must be established early in development

What patients/organisms?

Differentiation

Regulatory guidelines

Developing new antibiotics – HTL/LO



Challenges for SMEs in AMR R&D

Funding

- No/minimal revenue and lack of early-stage VC investment
- Reliant on non-dilutive and in-kind funding
- **Delays** waiting for grant decisions
- Spend more time raising money than on programs

Exit routes

- SMEs generally don't do commercialisation but look for deals with larger organisations
- Broken market = **Not enough major pharma acquisitions** of clinical-stage programs (some exceptions)

Risk

- **Portfolio size** and risk management
- Portfolio = lower risk, but more expensive and difficult to fund all
- Single asset or platform = higher risk, but easier to fund and progress

Capability

- Knowledge in-house vs expert consultants
- DMPK, In vivo, toxicology, clinical, CMC, human dose/PK prediction
- Build that **network**!

INFEX THERAPEUTICS

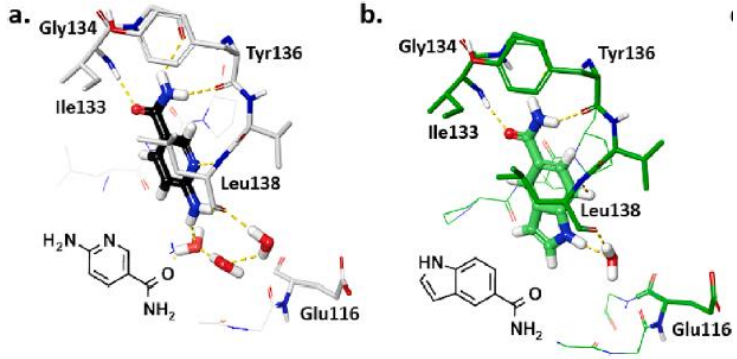
Case studies

INFEX Therapeutics

- SME based at Alderley Park, UK (~20 employees)
- Portfolio of infection and pandemic pathogen-focussed programs (AMR and antivirals)
- Discovery/hit findings > Phase 2 clinical POC
- Microbiology and synthetic/medicinal chemistry teams
- Expert network of consultants and CROs
- Non-dilutive and in-kind funding through iiCON, CARB-X, Innovate UK, NIAID

Case study 1 – TrmD inhibitors

- Early stage hit finding program into novel targets in Gram-negatives; collaboration with Lifearc
- TrmD identified as essential and a promising target
- Structure guided drug design
- Found in most clinically important Gram-negatives



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Evaluating the druggability of TrmD, a potential antibacterial target, through design and microbiological profiling of a series of potent TrmD inhibitors

Andrew J. Wilkinson [a,*], Nicola Ooi [a], Jonathan Finlayson [a], Victoria E. Lee [a], David Lyth [a], Kathryn S. Maskew [a], Rebecca Newman [a], David Orr [a], Keith Ansell [b], Kristian Birchall [b], Peter Canning [b], Peter Coombs [b], Lucia Fusani [b], Ed McIver [b], João Pisco [b], Philip M. Ireland [c], Christopher Jenkins [c], Isobel H. Norville [c], Stephanie J. Southern [c], Richard Cowan [d], Gareth Hall [d], Catherine Kettleborough [b], Victoria J. Savage [a], Ian R. Cooper [a]

Case study 1 – TrmD inhibitors

	TrmD IC_{50} (μM)[a]	MIC (μg/mL)[b]			Measured $LogD_{7.4}$
		H. Influenzae ATCC 49247	*E. coli* N43	*E. coli* N43 + PMBN (4 μg/mL)	
Control Antibiotics					
Erythromycin	ND[c]	4	8	0.5	ND[c]
Nicotinamide Series					
15	0.31	1024	>1024	>1024	1.0
21	0.011	1024	>1024	>1024	1.4
22	0.027	512	512	256	3.0
23	0.009	256	>1024	>1024	ND[c]
24	0.05	>1024	1024	1024	1.6
25	0.13	>512	>1024	>1024	1.0
Azaindole Series					
33	0.31	>1024	1024	1024	1.4
34	0.037	>1024	>256	>512	−0.2
35	0.039	>256	>512	>1024	ND[c]
36	0.036	>512	>512	>1024	0.2
37	0.013	ND[c]	>1024	>1024	−0.1
38	0.038	>1024	>512	>512	2.7
39	0.096	1024	>1024	>1024	ND[c]
40	0.12	>512	>1024	>1024	ND[c]

- Extensive effort into optimising enzyme potency, alongside antibacterial activity and cytotoxicity assays
- Despite highly potent compounds being generated, no significant antibacterial activity was observed
- Target essentiality? Target druggability?
- Findings published and program **terminated**

Case study 2 – MBL inhibitors

- Early-stage program developing hits as metallo-β-lactamase inhibitors
- Inhibitor to be used alongside β-lactams
- Several leads were identified and profiled

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Journal of Antimicrobial Chemotherapy

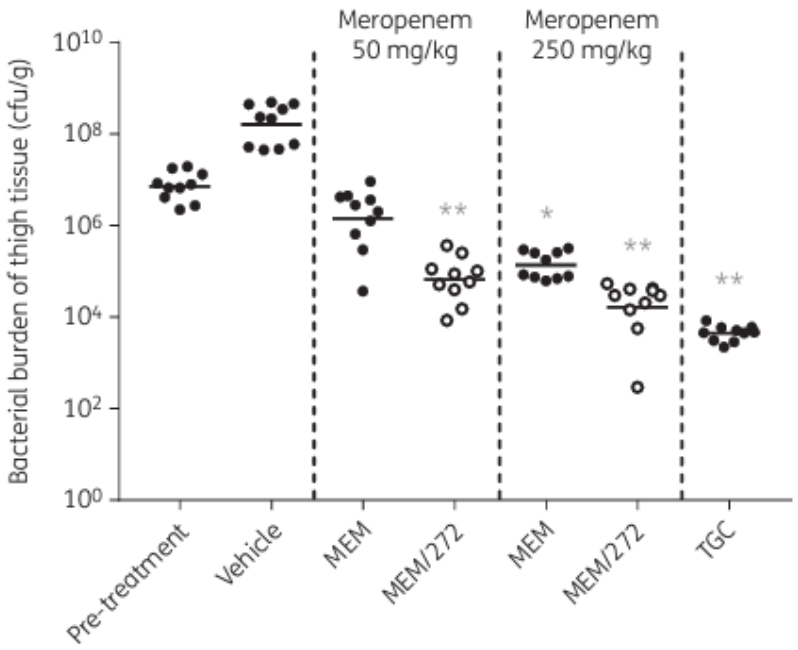
Restoring carbapenem efficacy: a novel carbapenem companion targeting metallo-β-lactamases in carbapenem-resistant Enterobacterales

Nicola Ooi[1], Victoria E. Lee [1], Nathan Chalam-Judge[1], Rebecca Newman[1], Andrew J. Wilkinson[1], Ian R. Cooper[1], David Orr[1], Sally Lee[1] and Victoria J. Savage [1]*

Table 1. Susceptibility of MBL-producing Enterobacterales to meropenem in combination with investigational MBLIs

	MIC (mg/L)						
Compound(s)	*E. coli* ATCC BAA-2452 (NDM-1)	*E. coli* NCTC 13476 (IMP)	*K. pneumoniae* ATCC BAA-2146 (NDM-1)	*K. pneumoniae* NCTC 13440 (VIM-1)	*K. pneumoniae* NCTC 13443 (NDM-1)	*K. pneumoniae* NCTC 13439 (VIM-1)	*E. coli* ATCC BAA-2469 (NDM-1)
272	>128	>128	>128	>128	>128	>128	>128
276	>128	>128	>128	>128	>128	>128	>128
364	>128	>128	>128	>128	>128	>128	>128
439	>128	>128	>128	>128	>128	>128	>128
MEM	**1**	**4**	**32**	**1**	**128**	**0.5**	**4**
MEM/272	0.03 (32)	0.03 (128)	0.25 (128)	0.06 (16)	4 (32)	0.06 (8)	0.06 (64)
MEM/276	0.06 (16)	0.03 (128)	0.5 (64)	0.06 (16)	16 (8)	0.06 (8)	0.06 (64)
MEM/364	0.06 (16)	0.03 (128)	2 (16)	0.06 (16)	8 (16)	0.12 (4)	0.12 (32)
MEM/439	0.06 (16)	0.06 (64)	2 (16)	0.25 (4)	16 (8)	0.25 (2)	0.06 (64)

Case study 2 – MBL inhibitors



- Additional optimisation to improve solubility
- **Preclinical candidate** selected – MET-X
- CTA/IND-enabling phase completed
- Phase 1 studies imminent for combination of meropenem and MET-X

Final thoughts….

- SMEs do the majority of preclinical innovation in AMR R&D
- There are numerous challenges for SMEs in developing AMR-focussed therapeutics
  - Funding, exit routes, management of risk and building a robust network of experts

Final thoughts….

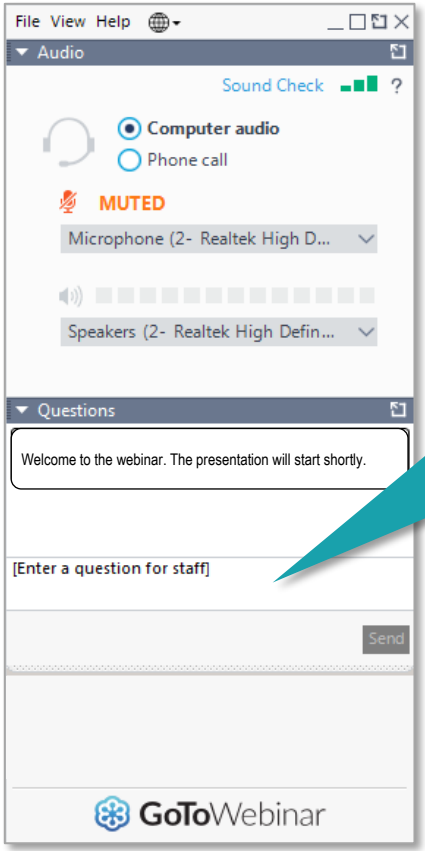
- SMEs do the majority of preclinical innovation in AMR R&D
- There are numerous challenges for SMEs in developing AMR-focussed therapeutics
  - Funding, exit routes, management of risk and building a robust network of experts
- However!!
- With a good team, innovative programs, flexible thinking and an enormous dose of optimism, these challenges can be overcome

INFEX THERAPEUTICS

Thank You!

How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

Progressing an antibacterial drug discovery project – an SME perspective

Alisa Serio
Executive Director of Microbiology and Nonclinical Development
Paratek Pharmaceuticals (USA)

Victoria Savage
Chief Scientific Officer
INFEX Therapeutics (UK)

Moderator & Host:
Daniel Ritz
Senior Director – Senior Group Leader
Biology Technologies/ Lead Discovery
Idorsia Pharmaceuticals (Switzerland)

Upcoming webinars

In collaboration with: AMR REGISTER A Vivli Initiative

The value of surveillance data in defining the medical need for new antimicrobials

With Ian Morrissey, Rebecca Li & Patricia Bradford

23 July 2024, 17:00-18:30 CEST

Exploring non-traditional antimicrobials: Insights from three cases

With Jennifer Schneider, Rida Mourtada & Gregorio Iraola

22 August 2024, 17:00-18:30 CEST

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