Progressing a discovery project – Criteria and challenges

Guest speakers: Ken Bradley & Diarmaid Hughes

Moderator: Karen Bush

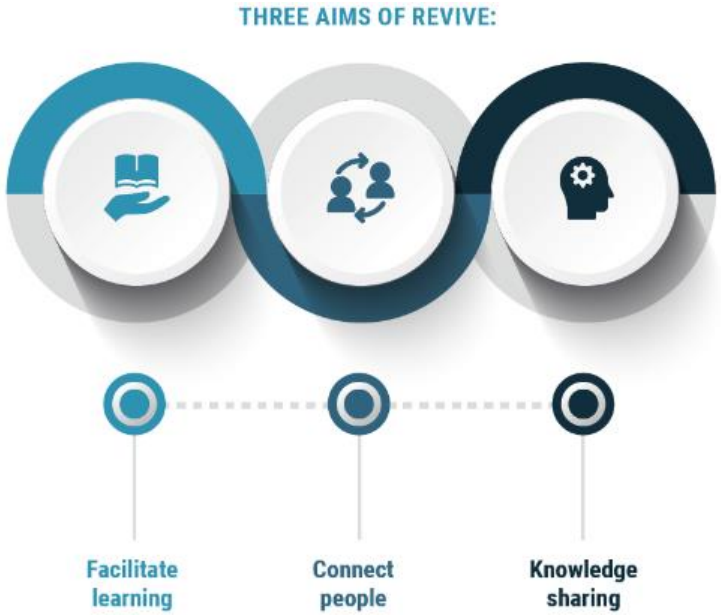
Host: Shirine Derakhshani (GARDP)

9 April 2024

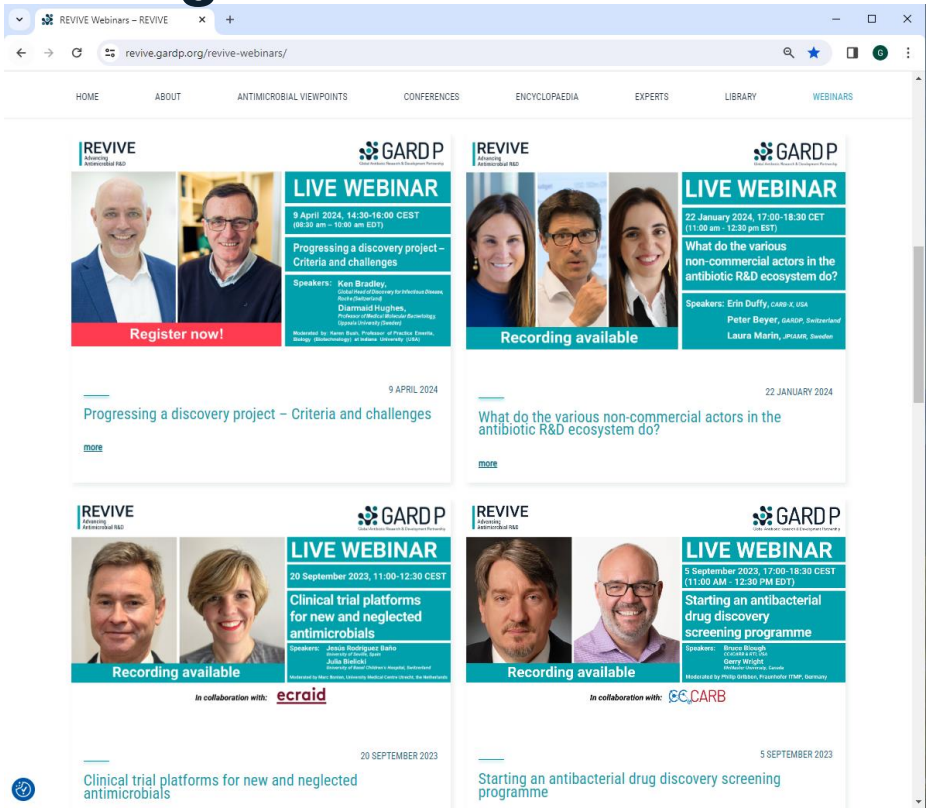
GARDP
Global Antibiotic Research & Development Partnership

REVIVE

Capture essential R&D technical knowledge and share expertise with the global community through the REVIVE website (revive.gardp.org).

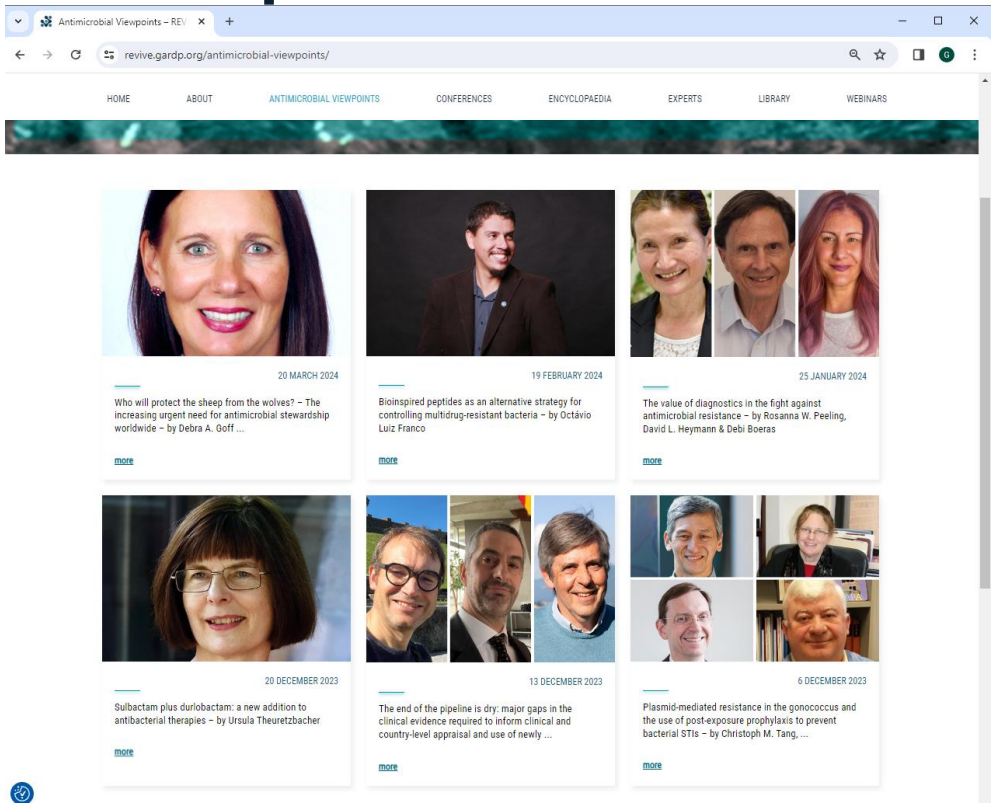


Webinar recordings



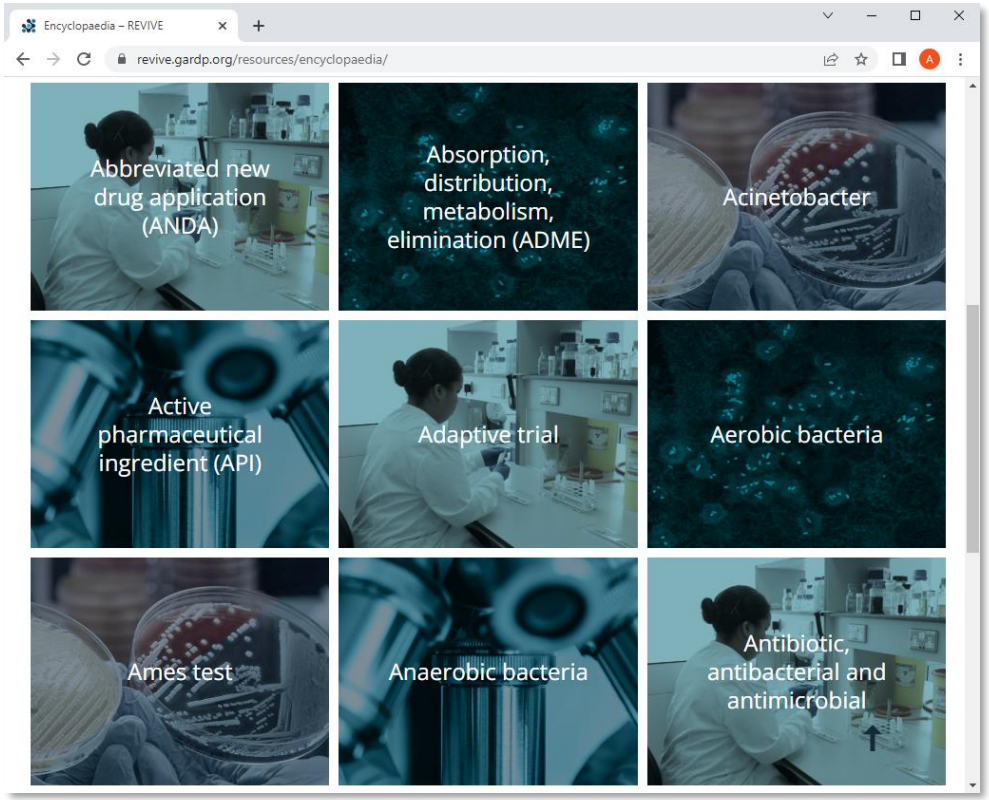
revive.gardp.org/webinars

Antimicrobial Viewpoints



revive.gardp.org/antimicrobial-viewpoints

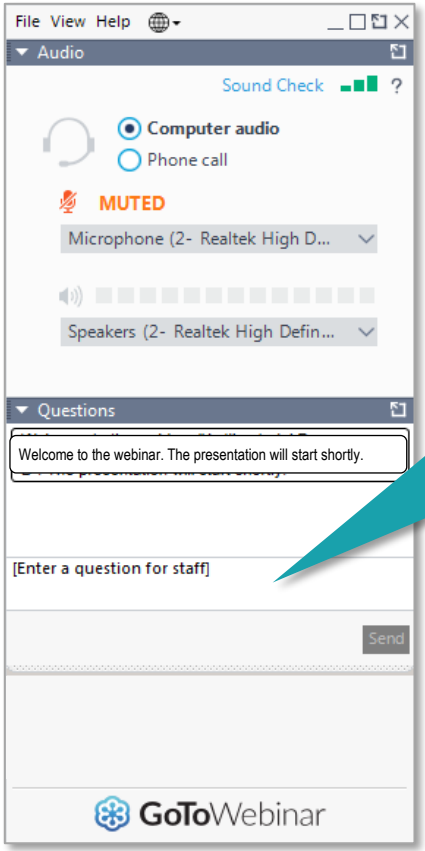
Antimicrobial Encyclopaedia



revive.gardp.org/resources/encyclopaedia

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 a discovery project – Criteria and challenges

Ken Bradley
Global Head, Infectious Disease Discovery
Roche (Switzerland)

Diarmaid Hughes
Professor of Medical Molecular Bacteriology
Uppsala University (Sweden)

Moderator:
Karen Bush
Professor of Practice in Biotechnology, Emerita
Indiana University (USA)

Ken Bradley

Ken Bradley is a pharma executive and scientist with a passion to bring novel therapeutics and cures to patients suffering from viral and bacterial diseases.

He is currently Vice President and Global Head of Infectious Disease Discovery at Roche Pharma Research and Early Development (pRED) in Basel, Switzerland.

Prior to joining Roche in 2015, Ken was Professor of Microbiology, Immunology and Molecular Genetics at the University of California, Los Angeles and Director of the Molecular Screening Shared Resource (MSSR) at the California NanoSystems Institute.

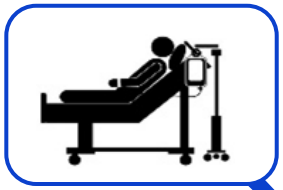
Progressing a discovery project – Criteria and challenges

Ken Bradley, PhD
Global Head, Infectious Disease Discovery

End-to-End decision making framework

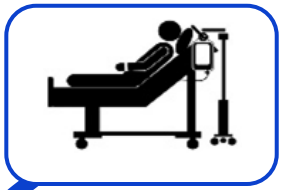
Starting and ending with the patient

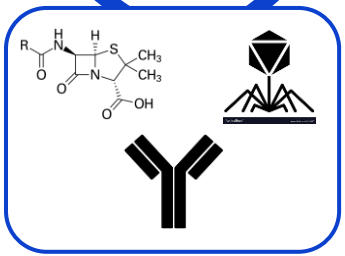
Define Patient & TPP



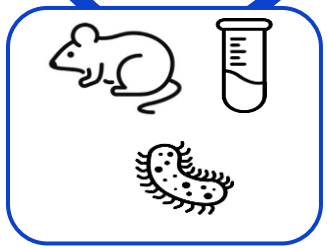
H2L→LO

Clinical Development





Modality Choice



Preclinical Studies

What Patients Population, Indications & Pathogens to Target

Development cost, duration and risks are highly dependant on patient population, indications and pathogens to cover

1 - What Patients are you after IV, oral, topical,.....

2 - What indications are you targeting

- **Hospital–acquired pneumonia**
- **Complicated Urinary tract infections**
- **Blood stream infections**

3 - What pathogens do you need to cover

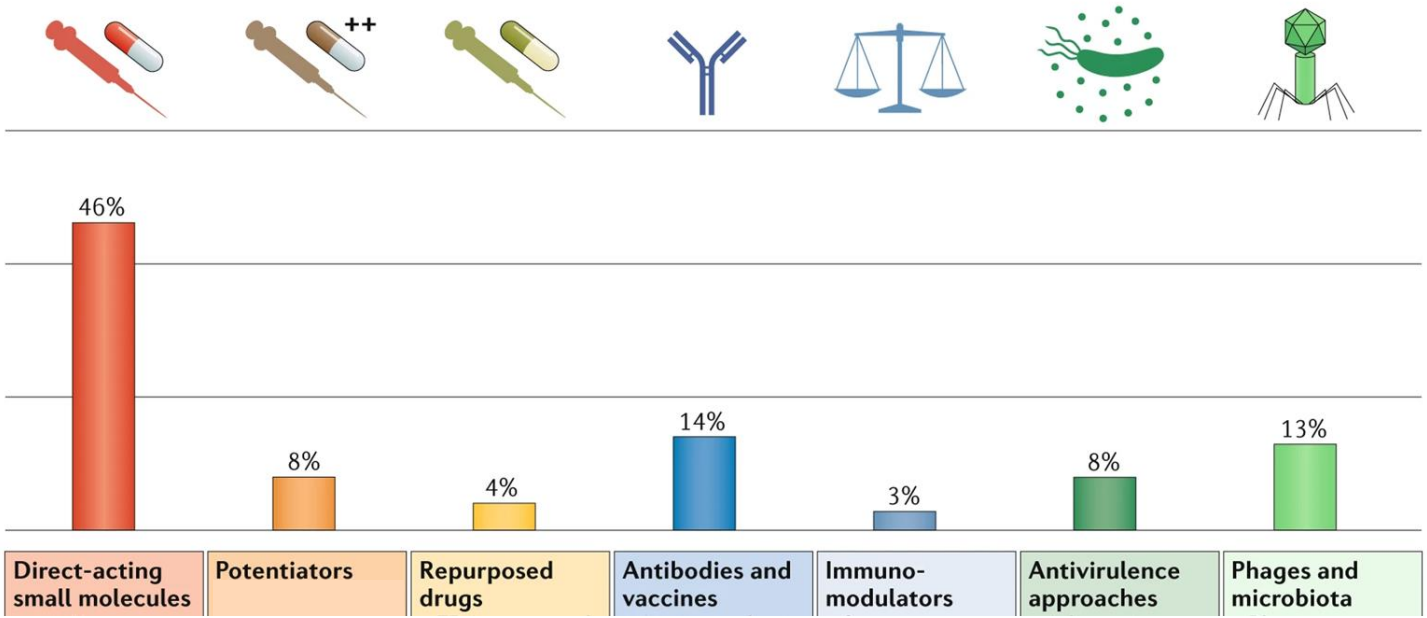
Gram negative: broad coverage vs single pathogen
(Enterobacteriaceae, Pseudomonas, Acinetobacter)

Gram positives MDR

NTM, TB, etc

Choose modality that addresses end-goal

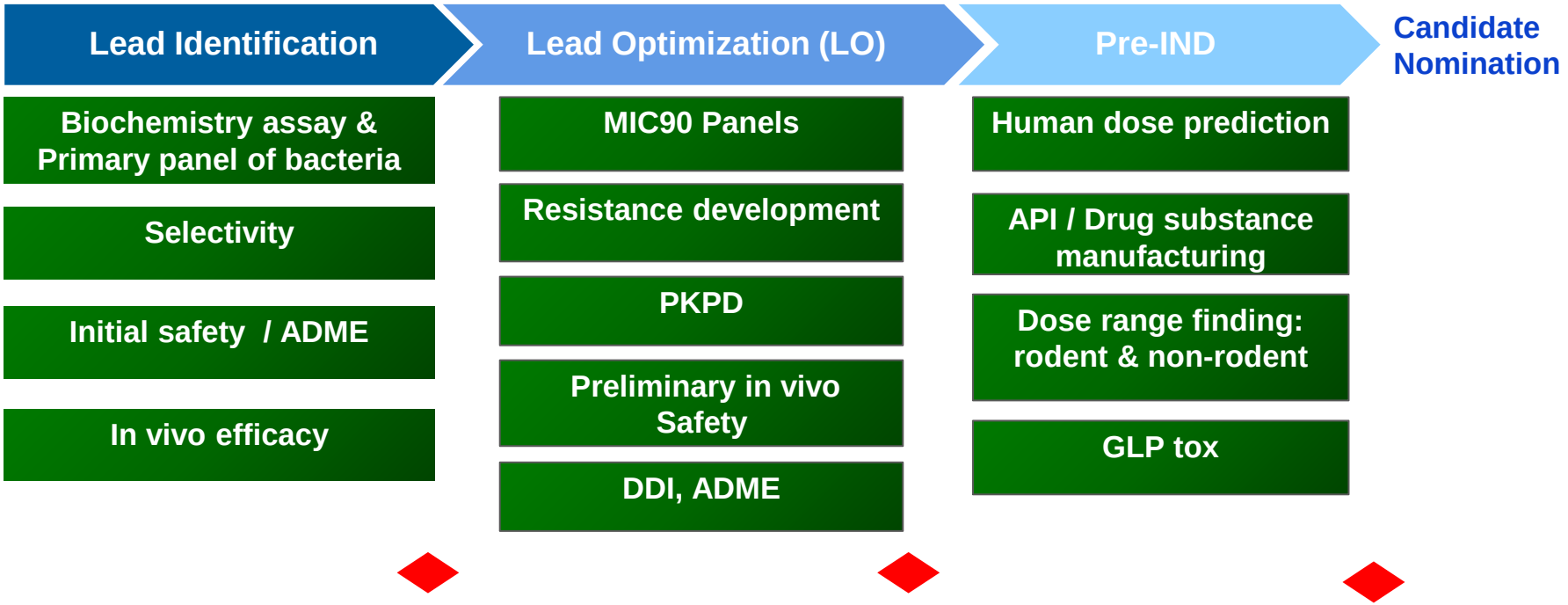
Direct acting small molecules most prevalent, but other modalities possible



*Nature Reviews Microbiology v18, pp275–285 (2020)

Set clear decision criteria for progression to candidate

Define a target candidate profile (TCP)



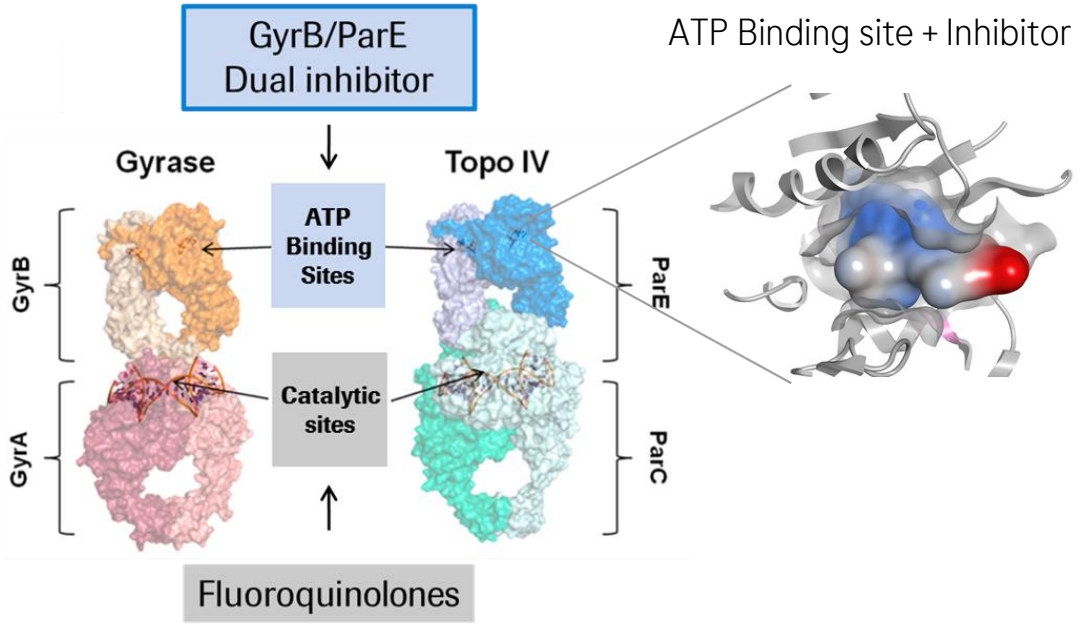
Decision making Example #1

GyrB/ParE inhibitors are attractive broad-spectrum candidates

Gyrase & Topo IV

- Clinically validated
- High level of conservation enables broad spectrum coverage
- Different mode-of-action to fluoroquinolones

TPP: must cover CRE, CRPA and CRAB and all pre-existing resistance mechanisms



“Go”based on balanced properties

Single criteria, i.e. MIC, not always key driver for “Go”

Table 2. Antibacterial GN Broad-Spectrum Coverage of Selected Compounds 10, 15, and 17

	MIC[a] *E. coli* strains (μg/mL)			MIC *K. pneumoniae* strains (μg/mL)			MIC *A. baumannii* strains (μg/mL)			MIC *P. aeruginosa* strains (μg/mL)		
Cmpd	ATCC 25922[b]	ATCC 35218[b]	ATCC BAA-2340[c]	ATCC 10031[b]	ATCC 700603[b]	ATCC BAA-2146[c]	ATCC 19606[b]	ATCC 51432[b]	ATCC BAA-747[c]	PAO-1[b]	ATCC 27853[b]	ATCC BAA-2113[c]
10b	0.5	0.76	0.76	0.09	0.76	3.02	0.76	3.02	3.02	2	0.76	0.76
10d	0.5	1.45	2.91	0.73	1.45	5.82	0.73	>23.3	1.45	2	5.82	1.45
10h	0.25	0.34	1.38	0.09	0.69	1.38	0.17	1.38	0.69	2	1.38	0.34
10i	0.25	2.85	2.85	0.178	1.42	5.7	1.42	5.7	2.85	2	2.85	1.42
10m	0.5	1.47	1.47	0.183	1.47	>23.5	073	>23.5	>23.5	4	>23.5	1.47
10t	0.25	0.75	0.75	0.38	0.75	1.5	0.38	1.5	0.75	2	1.5	0.75
15r	<0.25	1	2	<0.03	4	8	1	1	0.5	2	na	2
17r	0.31	3.13	12.5	<0.02	6.26	12.5	0.78	0.78	0.39	1.3	1.56	1.56
17x	0.81	5.56	2.78	0.09	22.2	22.2	5.56	5.56	2.78	10	11.1	11.1

[a]MIC: minimum inhibitory concentration. [b]Representative GN wide-type bacteria strains. [c]Representative GN MDR bacterial strain.

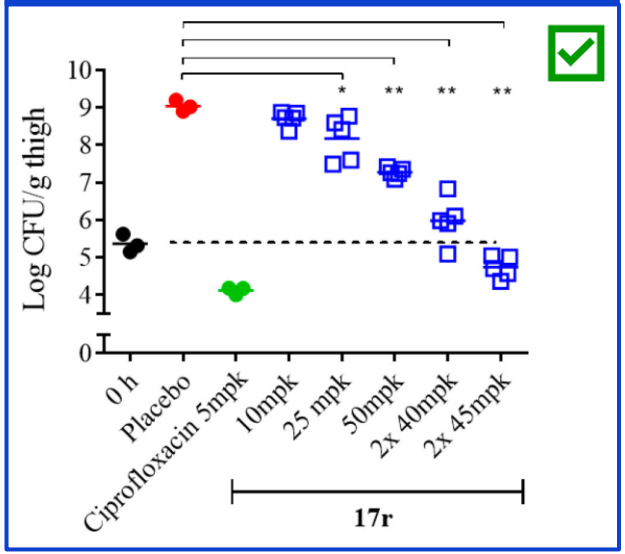
J. Med. Chem. 2020, 63, 17, 9623-9649

Initial *in vivo* study supports “Go”

Additional medchem needed to improve activity

Mouse thigh infection model

E. coli ATCC 25922



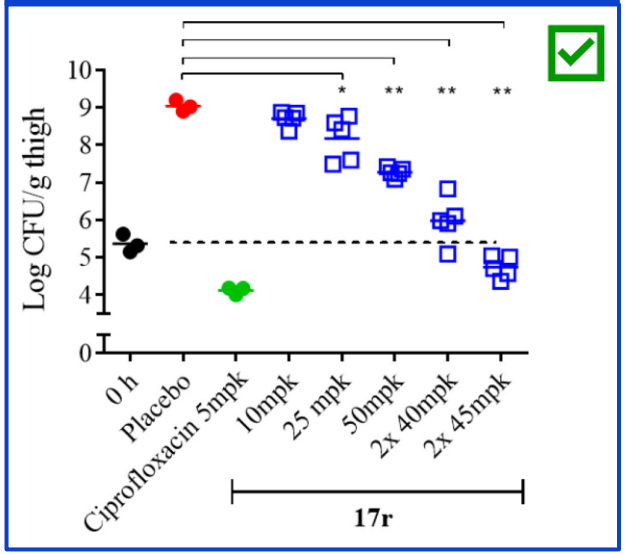
J. Med. Chem. 2020, 63, 17, 9623-9649

Improved compounds with better in vitro activity identified

Broad spectrum (in vitro) activity achieved

Mouse thigh infection model

E. coli ATCC 25922



	Main Go/NoGo Criteria	Cmpd A	Cmpd B
Broad spectrum activity	TPP: CRE+CRPA+CRAB		
	• In vitro: MIC ≤ 2ug/mL	Go	Go
Safety			

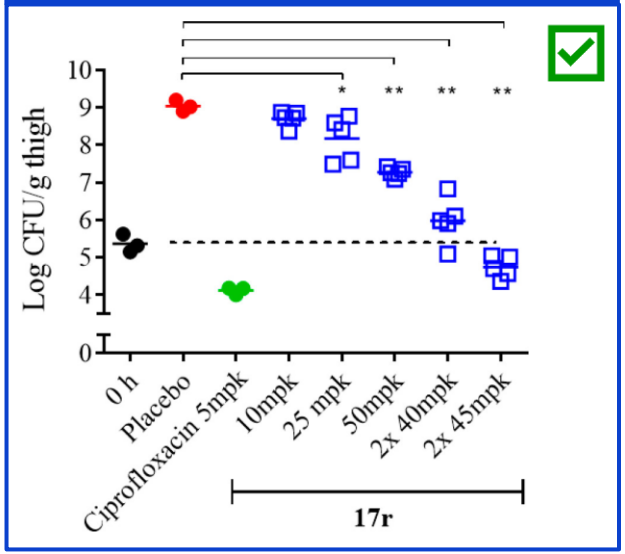
J. Med. Chem. 2020, 63, 17, 9623-9649

Advanced compounds do not meet TCP

Lack of activity in relevant model and safety limitations

Mouse thigh infection model

E. coli ATCC 25922



	Main Go/NoGo Criteria	Cmpd A	Cmpd B
Broad spectrum activity	TPP: CRE+CRPA+CRAB		
	• In vitro: MIC ≤ 2ug/mL • In vivo: lung model	Go No	Go No
Safety	Sufficient margin in minitox	No	No

J. Med. Chem. 2020, 63, 17, 9623-9649

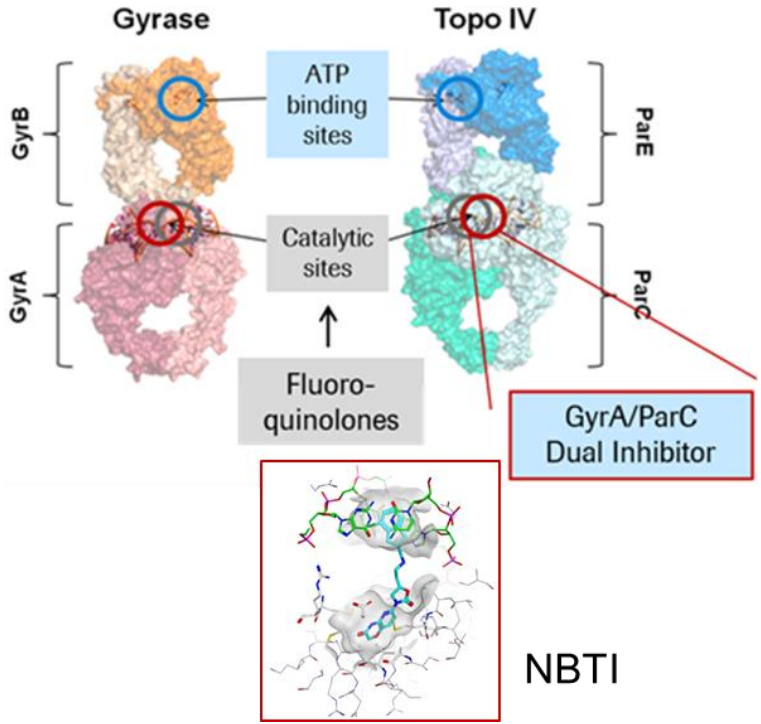
Decision making Example #2

GyrA/ParC inhibitors are attractive broad-spectrum candidates - NBTI example

Gyrase & Topo IV

- Clinically validated
- High level of conservation enables broad spectrum coverage
- Different mode-of-action to fluoroquinolones

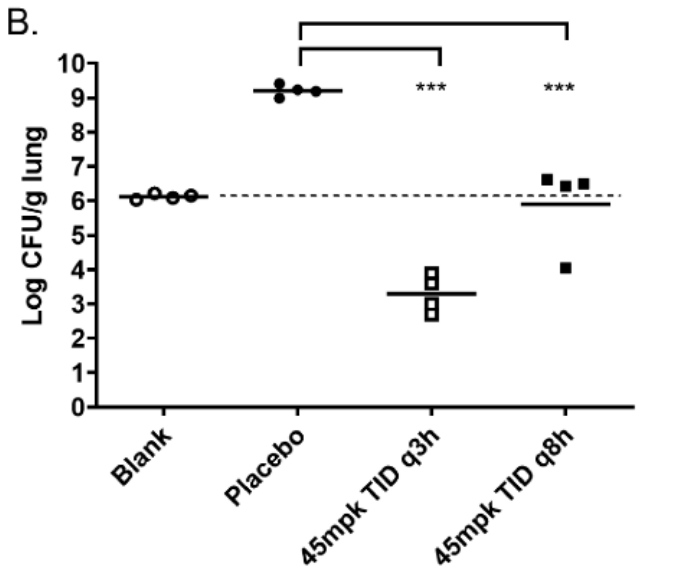
TPP: must cover CRE, CRPA and CRAB and all pre-existing resistance mechanisms



Decision point: preclinical efficacy and safety

Lead compound active in appropriate lung infection model

Pseudomonas lung infection model

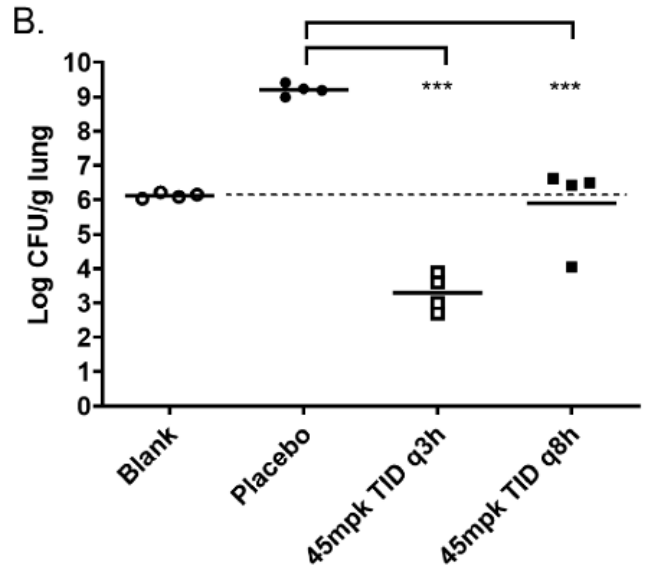


ACS Med. Chem. Lett. 2023, 14, 1791-1799

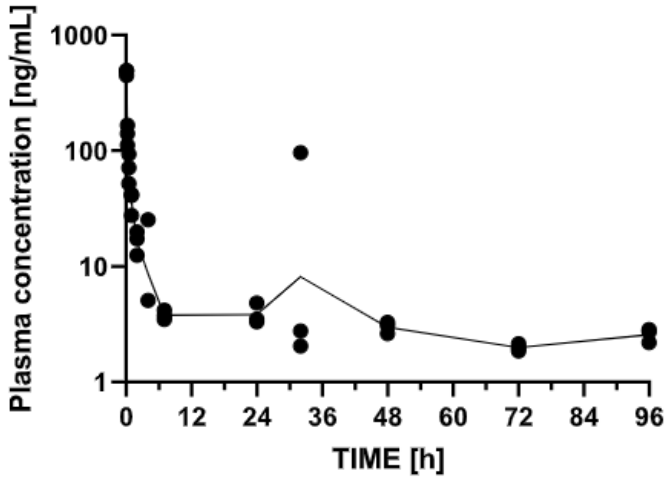
Decision point: preclinical efficacy and safety

"No Go" decision based on PK and developability challenges

Pseudomonas lung infection model



Rat single dose PK (iv)

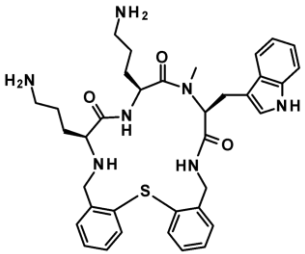


ACS Med. Chem. Lett. 2023, 14, 1791-1799

Decision making Example #3

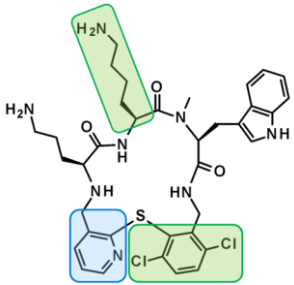
Zosurabalpin is a Novel Chemical Class, Pathogen-focused Antibiotic

Start of Program	**Go/No-Go**	**"Go"**	**Clinical Development**
Acquisition of macrocycle technology from Tranzyme	Safety/Developability Issue	Preclinical Development	First in human NCT04605718



HTS hit

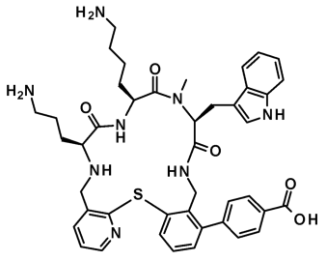
Phenotypic screening identifies compounds with pathogen-specific antibacterial activity



1st generation lead

(basic)

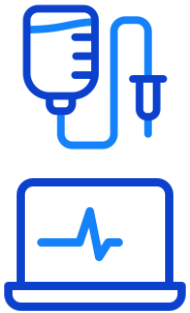
Morbidity, mortality in rats hypothesized to correlate with *in vitro* plasma lipid precipitation



clinical lead - Zosurabalpin (RG6006)

(zwitterionic)

Improved tolerability for Zwitterionic MCPs



Phase 1 clinical studies initiated

Nature v 625, pp 566–571 (2024); Nature v 625, pp 572–577 (2024)

Doing now what patients need next

Diarmaid Hughes

Diarmaid Hughes is Professor of Medical Molecular Bacteriology at Uppsala University, Sweden.

He has been working actively within the Innovative Medicines Initiative (IMI), New Drugs for Bad Bugs (ND4BB), ENABLE Project since its beginning in February 2014. Since the IMI ENABLE project ended in 2021 the Swedish government has funded a smaller-scale continuation project, ENABLE-2, to maintain essential parts of the antibiotic discovery platform. ENABLE-2 supports antibiotic Hit to Lead projects from academic groups throughout Europe. Diarmaid Hughes is co-coordinator of ENABLE-2.

Diarmaid's research interests outside ENABLE include bacterial evolution and physiology with a particular interest in the evolutionary trajectories to antibiotic resistance, and how resistance affects relative biological fitness. He has published over 100 original research articles and numerous reviews, many on antibiotic resistance evolution.

He holds a PhD in Genetics from Trinity College Dublin and is a Fellow of the American Academy of Microbiology.

UPPSALA UNIVERSITET

REVIVE Webinar

Progressing a Discovery Project – Criteria and Challenges

Progression criteria and Go/NoGo decisions in antibacterial drug discovery – an academic view

Diarmaid Hughes
Prof. Medical Molecular Bacteriology
Dept. Medical Biochemistry & Microbiology
Uppsala University, SWEDEN

UPPSALA
UNIVERSITET

Diarmaid Hughes
Co-coordinator of ENABLE-2

Coordinator (Anders Karlén)

ENABLE-2

Antibacterial Drug Development Engine

UPPSALA UNIVERSITET

ENABLE 2014-2021

Consortium with 50 partners:

Public partners (13 European countries)
Uppsala University managing entity
- ***24 academic/institute/hospital organizations/non-profits***
- ***22 SMEs***

Private partners (EFPIA)
GlaxoSmithKline, Pennsylvania, US
GSK, Evotec, Basilea & AZ

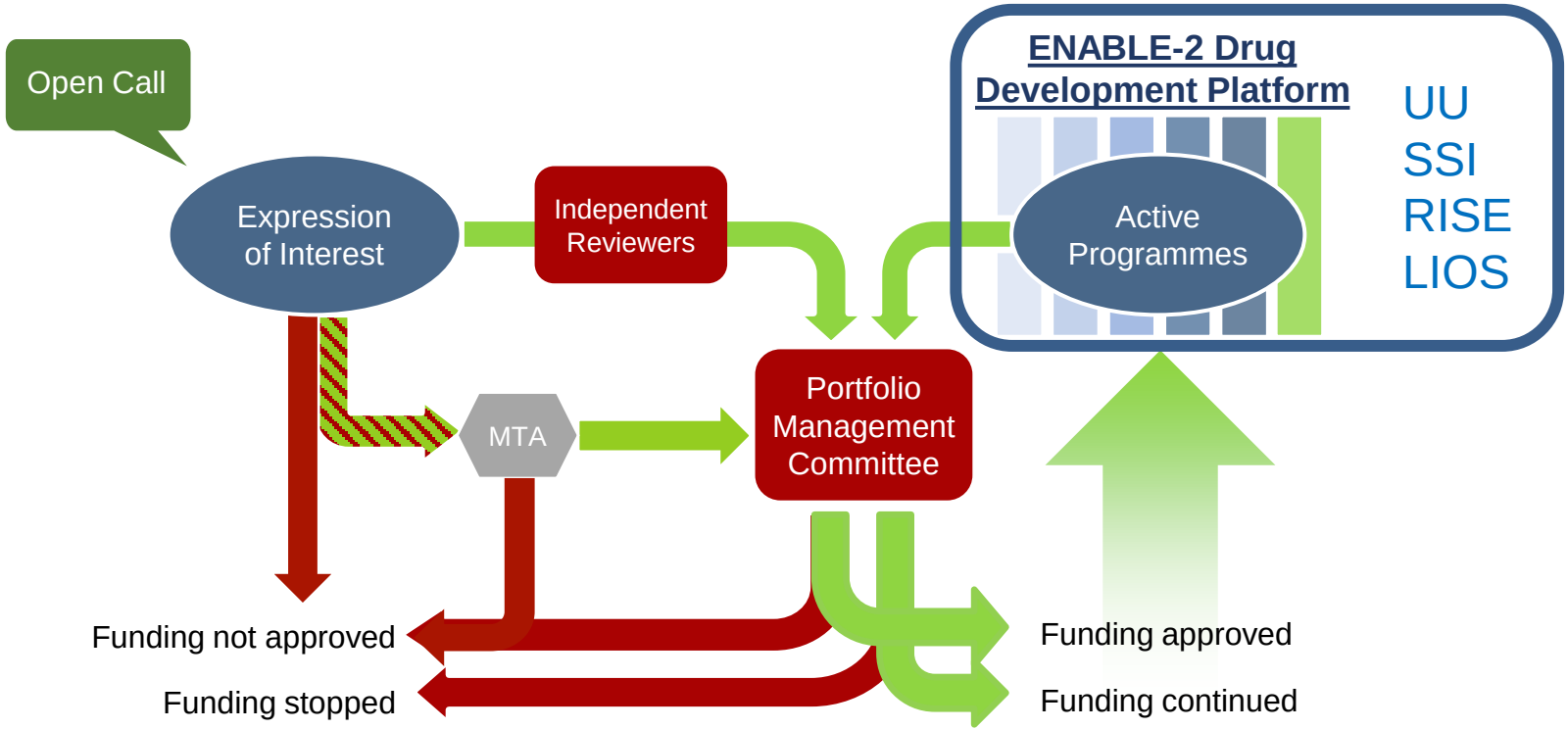
Launched Feb 2014, 7,5 year run time
- ***Projected budget: €85 million (€58.9 IMI funding)***

Goals

- Create a collaborative drug development platform
- Identify three Leads
  - ✓ 5 Leads identified (aim 3)
- Identify two Development Candidates
  - ✓ 3 Development Candidates identified (aim 2)
- Progress at least one compound into Phase 1
  - ✓ 1 compound finalized Phase 1 studies (aim 1)

UPPSALA UNIVERSITET

ENABLE-2 (2021 -) an Antibiotic Discovery Engine Open to Academic Researchers in Europe



UPPSALA UNIVERSITET

Challenges for Antibiotic Discovery in Academia

Funding

Planning versus Serendipity

Expert Advice on Development Paths

I will touch on each of these points during the talk

UPPSALA UNIVERSITET

Typical Academic Research Funding Model

1. Research grants awarded on the basis of:
   'scientific excellence' → 'groundbreaking' results → 'high profile' publications

2. Awarded to individual researchers
   Academia prioritizes individual excellence over teamwork

3. Awarded for a set period
   Often 3 – 5 years, regardless of the short-term results

Ways out of this dilemma?
   Funding for collaborative projects (EU, or National Strategic Funding)
   ENABLE and similar projects

UPPSALA UNIVERSITET

Typical Academic Research Funding Model

1. Research grants awarded
   - breaking" results → 'high profile' publications
2. Awarded to individual
   - excellence over teamwork
3. Awarded for a set period
   - short-term results

Ways out of this dilemma?

Funding for
- ategic Funding)

Antibiotic discovery: Groundbreaking or doing the same old thing?

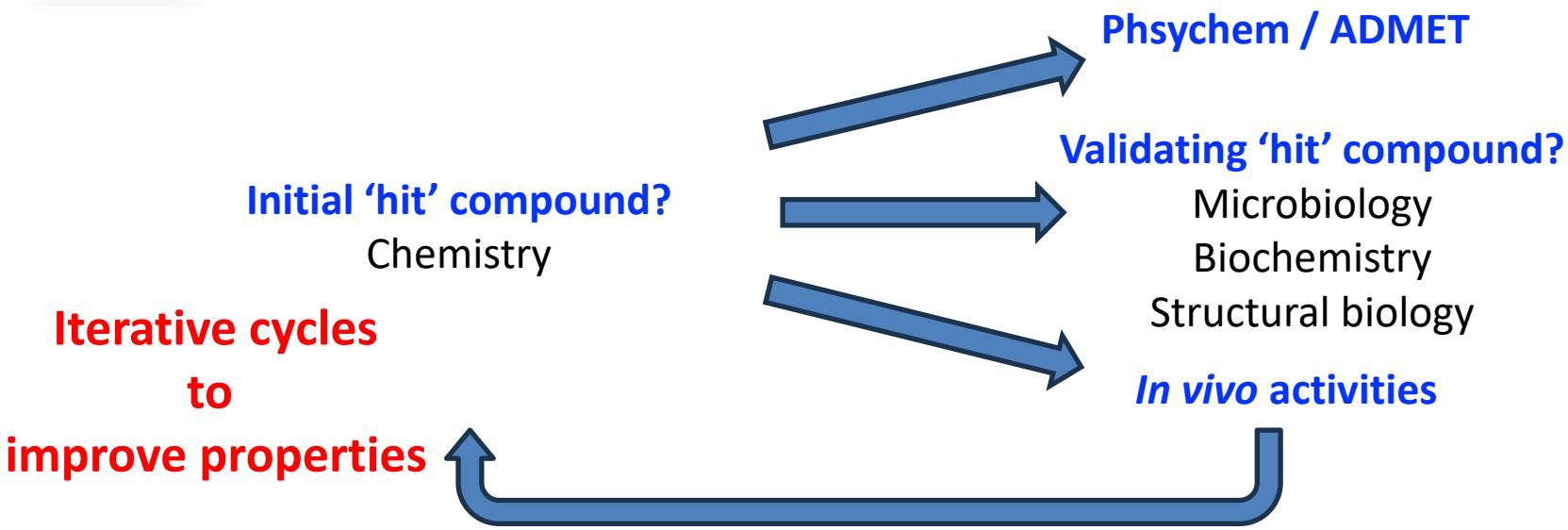
Antibiotic discovery is multidisciplinary, depends on teamwork

Long timelines & high failure rates – not what the university wants!

Side projects – slow progress, need TCP/TPP advice & collaborators

UPPSALA UNIVERSITET

Antibiotic Discovery is Multidisciplinary



Dilemma: 'Star' Researcher versus Collaborative Team

UPPSALA UNIVERSITET

Planning versus Serendipity in Academia

Project initiation in Big Pharma usually based on forward planning

(i) Medical need, Market research, Portfolio management, etc

(ii) Figure out how to discover starting ‘actives’

Library screening

Acquire/licence an existing active (SME, academic, etc)

Project initiation in Academia is often based on serendipity

(i) Exploit ‘actives’ that have been found (often by chance)

(ii) Figure out what to do next and how to do it!

UPPSALA UNIVERSITET

Project Initiation in Academia

Chemists/Medicinal chemists
Making libraries - discover ‘actives’

Biochemists/Structural biologists
Target-based design/FBDD/DEL - discover ‘actives’

Molecular Microbiologists
Soil microorganisms - discover ‘actives’

UPPSALA UNIVERSITET

Project Initiation in Academia

Chemists/Medicinal chemists
Making libraries - discover ‘actives’

Bi… …logists
…ed design/FBDD/DEL - discover ‘acti…
…logists
…il microorganisms - discover ‘actives’

‘Basic research’ or ‘technology development’ – primary aim is publication

Big decision! – explore ‘actives’ to initiate an antibiotic project

UPPSALA UNIVERSITET

Academics and Project Direction

Naïve:	It's all about killing bacteria – low MIC It's all about doing clever chemistry It's all about getting a good enzyme inhibition It's all about high resolution structures
Awakening:	Does it clear infection in an animal?
Excited:	Could it clear infection in humans?
Expert advice:	Where is the project heading? How will the project get there?

Getting expert advice and criticism is essential

UPPSALA UNIVERSITET

Where can Academics find Expert Guidance?

Literature reviews by antibiotic discovery & development experts

Ad hoc meetings with experts (e.g., at conferences)

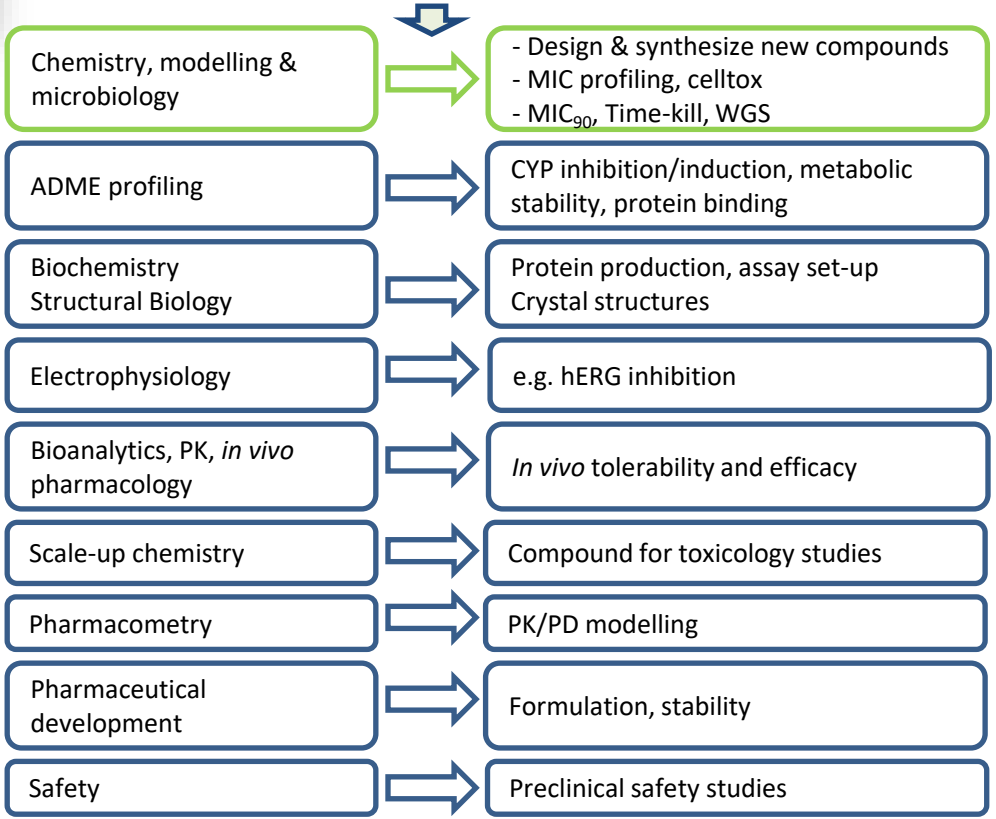
Direct regular contacts with experts – e.g., via ENABLE membership

Catch 22: May need a developed program to gain this access

UPPSALA UNIVERSITET

Discovery Cascade for New Antibiotics

Identifying chemical starting points (HIT discovery) (Research Councils) – but who funds & guides the next stages?



<u>Developing an antibiotic requires</u>;

- **Experienced collaborators**
- **Expertise in antibiotic drug discovery and development**
- **Time**
- **Money**

UPPSALA UNIVERSITET

TCP - cascades of assays, values to achieve Go/NoGo decisions

Chemistry
- Chemical Synthesis
- Kinetic solubility
- Thermodynamic solubility
- Chemical stability
- Scale-up chemistry

In vivo
- Preformulation
- Mouse tolerability
- Maximum tolerated dose
- Mouse PK
- Mouse infection models

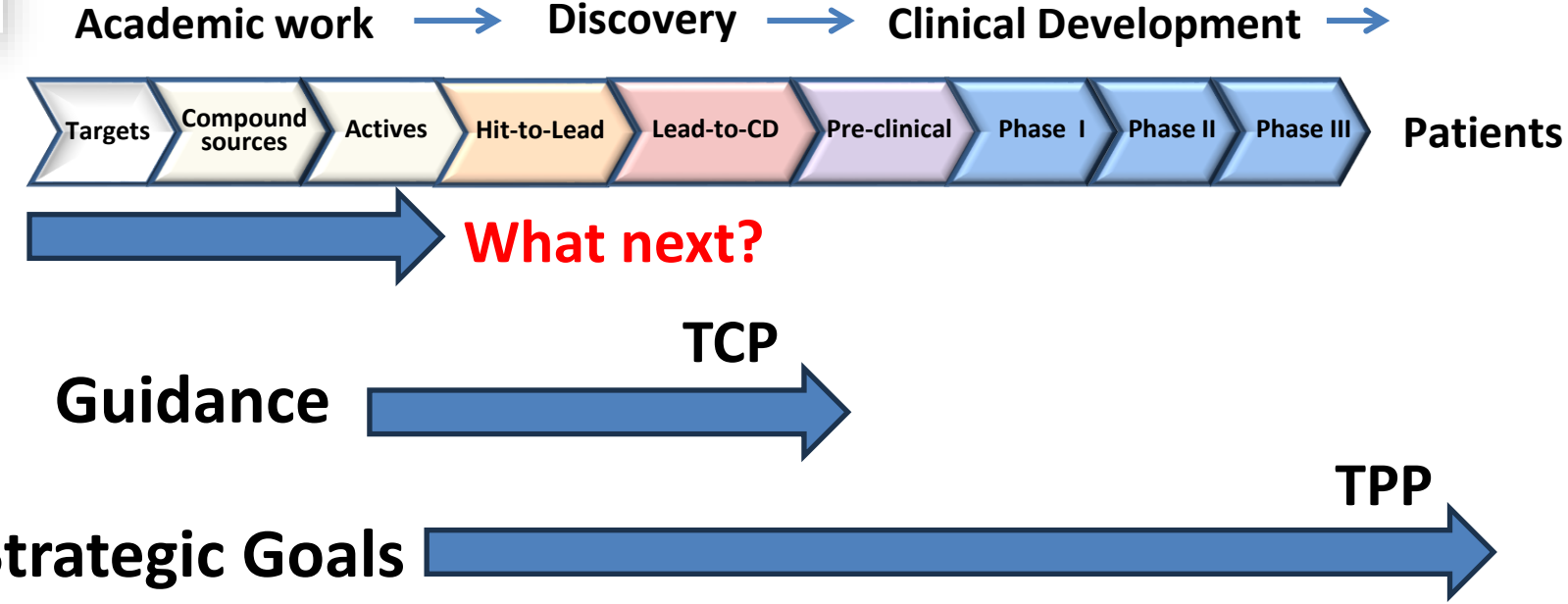
ADMET etc
- CYP3A4 inhibition
- hERG/NaV1.5/CaV1.2
- Microsomal stability (h,m,r)
- Metabolite profiling
- Hepatocyte stability
- Protein binding
- CYP1A2, 2C9, 2D6 inhibition
- CYP3A4 induction
- Caco 2 permeability

Microbiology
- MIC primary panel
- MIC challenge panel
- MIC90 panels
- Haemolysis
- Cytotoxicity
- Time-kill assays
- Resistance mechanism (WGS)
- Resistance development & fitness

Off target effects
- CEREP profiling
- AMES, mouse lymphona assay

Guiding academics – can be like herding ‘curious’ cats

UPPSALA UNIVERSITET



Projects such as ENABLE work with industry-aligned TCP's and TPP's
Academics need expert guidance to get beyond the 'actives' stage

UPPSALA UNIVERSITET

Conclusions: Academics (and to some extent SME's)

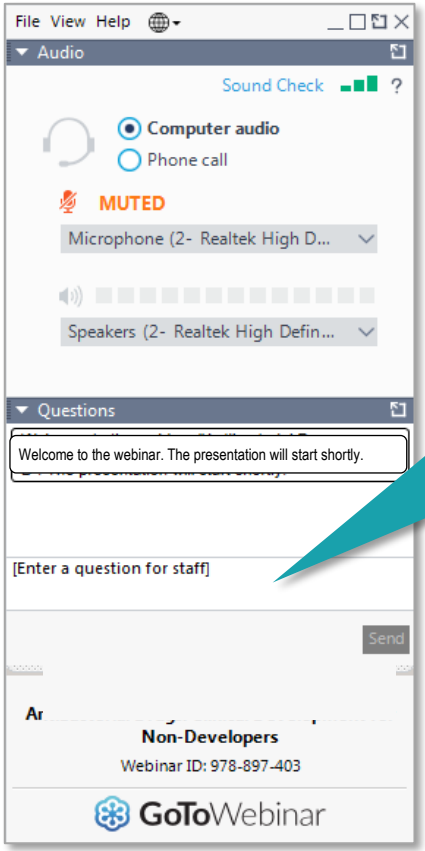
Positives:
New and varied ideas on drug discovery
Actual starting point molecules
Technical abilities (but in limited areas)

Negatives:
Poor knowledge of development paths (TCP)
Poor appreciation of development goals (TPP)
Lack of funding/access to required assays
Pressure to Publish or Patent too early

Academics need:
Access to advice on TPP's and TCP's
Access to funding for H2L exploration via TCP's

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 a discovery project – Criteria and challenges

Ken Bradley
Global Head, Infectious Disease Discovery
Roche (Switzerland)

Diarmaid Hughes
Professor of Medical Molecular Bacteriology
Uppsala University (Sweden)

Moderator:
Karen Bush
Professor of Practice in Biotechnology, Emerita
Indiana University (USA)

Upcoming webinars – 23 April

Check out the latest REVIVE updates

- On the REVIVE website (revive.gardp.org/webinars)
- In our newsletters
- On Twitter and LinkedIn

Thank you for joining us