DNDi: Global Antibiotic R&D (GARD) Partnership Scientific Consultation, Institut Pasteur, Paris, 29 February 2016

Antibiotic Resistance Breakers for Use in Combinations

Dr David Brown PhD, FRSC, FRSM
Antibiotic Research UK.
Trustee. Chair of Scientific and Technical Advisory Committee.
davidbrown1000@btinternet.com

The world's first charity developing antibiotics against antibiotic resistant bacteria

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DEVELOPING NEW ANTIBIOTICS

Our People

Dr David Brown
Trustee / STAC
Principal, Alchemy Biomedical Consulting

Ashley Burgess
Chair Trustees and Finance Raising Committee
Chairman, Burgess Group plc

Dr Lloyd Czaplewski
STAC
Chief Scientific Officer, Persica Pharmaceuticals

Professor Anthony Coates
Trustee / STAC
Professor of Medical Microbiology, St. Georges London University

Professor Chris Dowson
Trustee / STAC
Professor of Microbiology, Warwick University

Professor Colin Garner
Chief Executive / Trustee / STAC
Honorary Professor, Hull York Medical School, York University

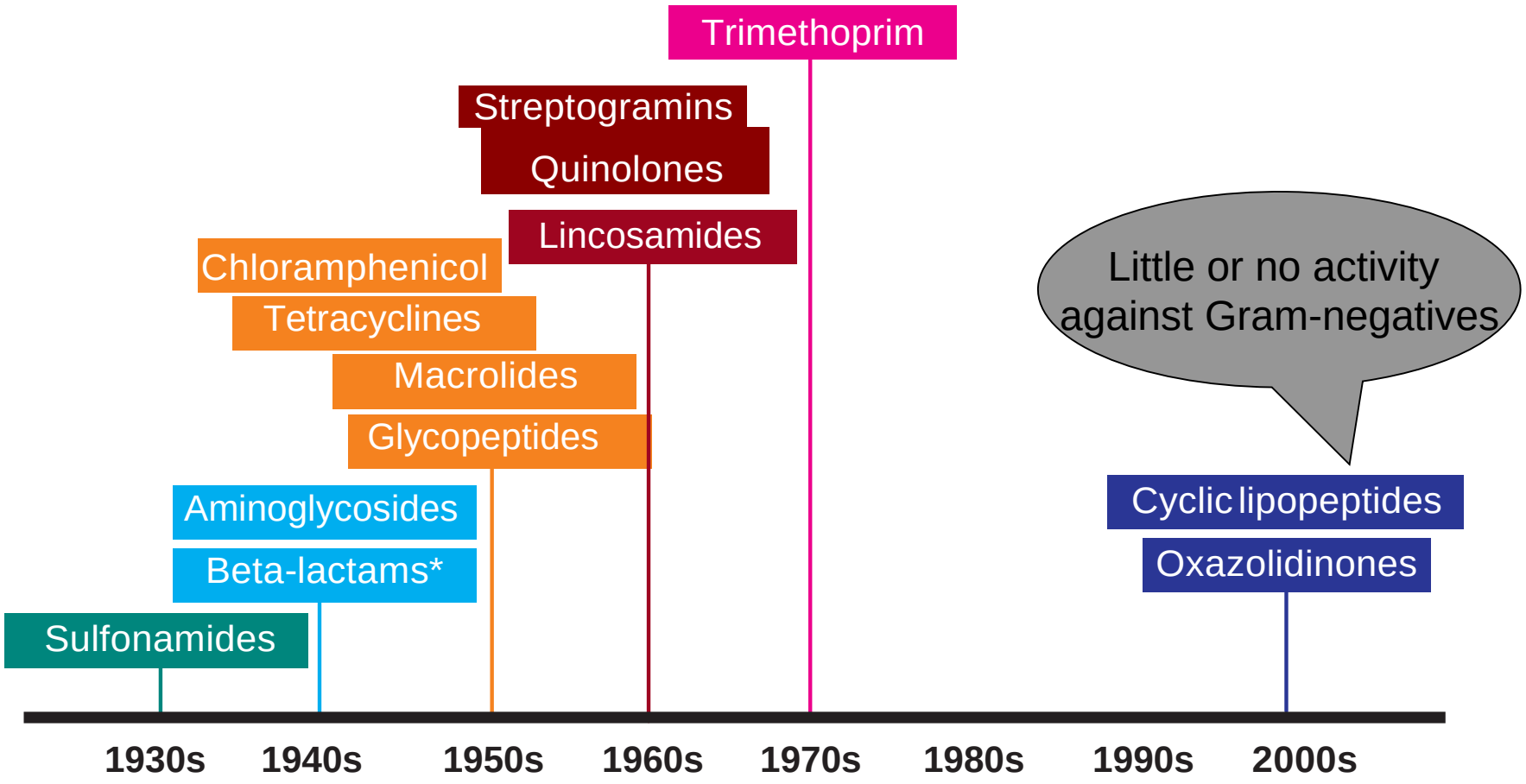
Professor Mark Moloney
STAC
Professor of Chemistry, Oxford University

Professor Neil Woodford
Head AMRHAI, PHE, London

Dr David Roper
STAC
Reader in Microbiology, Warwick University

Dr Tim Tasker
STAC
Chief Medical Officer, Heptares Pharmaceuticals

Focus initially on antibiotics against Gram-negative bacteria.
No new chemical classes since 1970s.



World Health Organization

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What are Antibiotic Resistance Breakers (ARBs)?

- There may be opportunity to break resistance by repositioning certain marketed non-antibiotic drugs for co-administering with existing antibiotics.

- Concept well-proven with beta-lactamase inhibitors, but...
  there are now ~1600 known beta-lactamases AND many other resistance mechanisms.

- We need alternative approaches to breaking resistance.

- A growing literature indicates that several non-antibiotic drugs can be additive to or synergise with antibiotics to reduce MICs and thereby reverse resistance.

- These Antibiotic Resistance Breakers could provide a rapid contribution towards solving the antibiotic resistance problem.

- In addition, combinations of 2 or 3 antibiotics have not been explored thoroughly. We will do this also. And 'sequential antibiotics'

Some of our ideas are described in my recent review article. Nature Reviews Drug Discovery, December 2015

OPINION

Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void?

David Brown

Abstract | Concern over antibiotic resistance is growing, and new classes of antibiotics, particularly against Gram-negative bacteria, are needed. However, even if the scientific hurdles can be overcome, it could take decades for sufficient numbers of such antibiotics to become available. As an interim solution, antibiotic resistance could be 'broken' by co-administering appropriate non-antibiotic drugs with failing antibiotics. Several marketed drugs that do not currently have antibacterial indications can either directly kill bacteria, reduce the antibiotic minimum inhibitory concentration when used in combination with existing antibiotics and/or modulate host defence through effects on host innate immunity, in particular by altering inflammation and autophagy. This article discusses how such 'antibiotic resistance breakers' could contribute to reducing the antibiotic resistance problem, and analyses a priority list of candidates for

for patients with septicaemia due to MDR *Escherichia coli*[3]. Data from the USA show a similar pattern. The 2013 report from the CDC highlighted carbapenem-resistant Enterobacteriaceae (CREs) as an urgent threat[4]. In Asia, substantial resistance has emerged in both India and China, with resistance levels reported in the range of 50–80%. This has caused increased use of carbapenems, which were previously reserved for extreme cases of infection in the very sick, the immune-compromized or as a last resort. Now, bacteria have adapted and selected for carbapenem-destroying enzymes, known as carbapenemases, and few antibiotics remain effective against these CREs. *K. pneumoniae*, *E. coli*, *P. aeruginosa* and *A. baumannii* produce metallo-β-lactamases such as *K. pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) — enzymes that degrade numerous antibiotics containing a β-lactam ring, such as penicillins, cephalosporins and carbapenems. Bacteria carrying the genes that encode these enzymes are becoming resistant to all

A review of antibiotic combinations, and sequential use of antibiotics, is currently being prepared for publication.

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ARBs are attractive for several reasons:

(a) we do not know if it is feasible to discover the new chemical classes of antibiotics required in the 21st century;

(b) even if it is possible, the costs will be high and the timelines uncertain;

(c) repurposing drugs as ARBs overcomes many of the commercial barriers to developing new antibiotics;

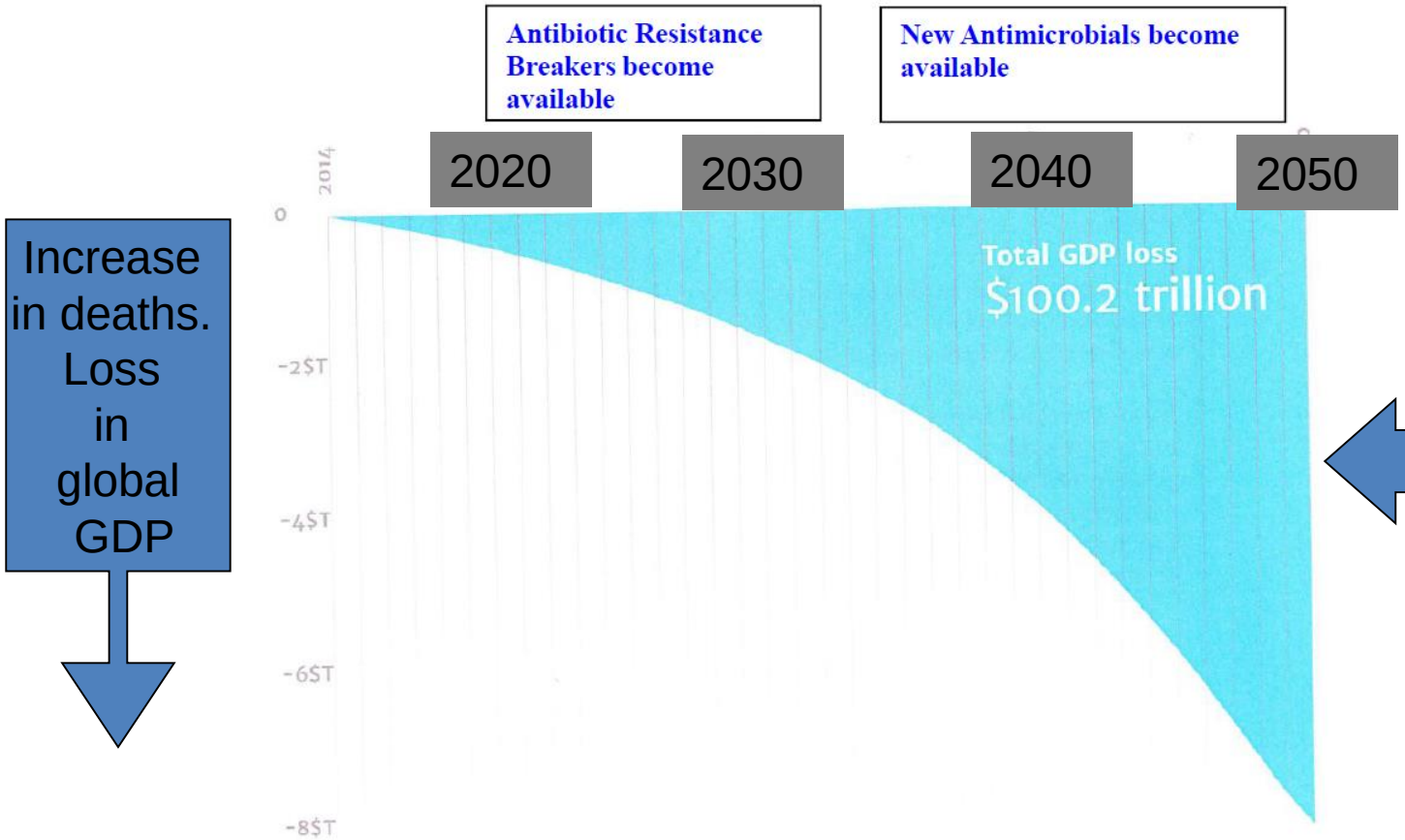
(d) a few ARBs, developed at low cost, could salvage many of the 200 or so existing antibiotics;

(e) if each ARB could be used with more than one antibiotic, the costs and the risks would decrease after the first combination had been developed;

(f) if resistance develops to the first ARB combination, a second ARB could rescue the same antibiotic. This cycle could be repeated many times, enabling old antibiotics to be used far into the future.

Why Antibiotic Research UK is focusing on ARBs:

ARBs MUST fill the gap before invention of new antibiotics



Increase in deaths. Loss in global GDP

From the O'Neill report, 12/2014

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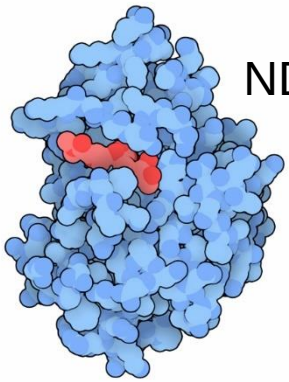
The resistance problem in more detail

- European and US data indicate growing resistance to cephalosporins, fluoroquinolones and aminoglycosides, and a 30% mortality rate for patients with septicaemia due to MDR *E. coli*

- Asia, India and China have even higher rates of resistance to these classes, with levels reported in the range 50% to 80%.

- This has caused increased use of carbapenems and is selecting for carbapenem-resistant Enterobacteriaceae (CREs; especially *K. pneumoniae* and *E. coli*) and other carbapenem resistant organisms (including *P. aeruginosa* and *A. baumannii*), many of which produce carbapenemases.

The resistance problem in more detail (contd)


NDM-1

- The most widely reported carbapenemases are
  KPC (*Klebsiella pneumoniae* carbapenemase),
  NDM (New Delhi Metallo-beta-lactamase),
  VIM (Verona Integron-Mediated Metallo-beta-lactamase)
  OXA-type
  IMP enzymes.
- They are encoded by genes transferable between bacteria, which greatly facilitates spread.
- CREs have been labeled "one of the three greatest threats to human health" by the World Health Organization and others.
- Pathogens carrying these resistant carbapenemases cause many types of infections in the urinary tract, lungs, blood, and other organs. Patients with serious CRE infections have high mortality.

ANTRUK's Research Programmes

- Raised sufficient funds to begin initial research programmes
- Call for Proposals by end March 2016 (contractors to run assays)
- Aim to complete *in vitro tests* during 2016
- Title of Project: Evaluating non-antibiotic drugs as 'Antibiotic Resistance Breakers': a comprehensive study to examine approved drugs to overcome multidrug resistance in Gram-negative bacteria

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KEY GOALS

(i) to comprehensively screen marketed drugs for ability to rejuvenate the activity of 4-6 antibiotics against 4 Gram-negative MDR bacterial pathogens to establish the scale of the ARB opportunity;

(ii) to provide robust *in vitro* data to demonstrate Proof- of-Concept for the ARB approach and to place the information into the public domain to inform and influence wider antibiotic research;

(iii) to identify if any of the antibiotic-ARB combinations merit further progression towards clinical trials.

ANTRUK's Research Programmes

TARGET GRAM – NEGATIVE SPECIES

Multidrug-resistant strains of

Klebsiella pneumoniae

Escherichia coli

Pseudomonas aeruginosa

Acinetobacter baumannii

- All strains to be tested will have molecularly characterised resistances and comprehensive antibiotic sensitivity/resistance profiles

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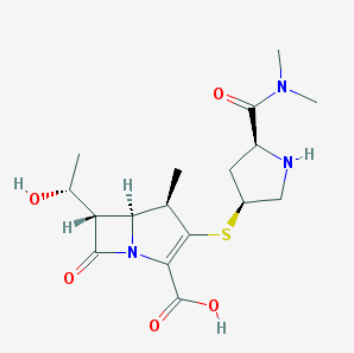
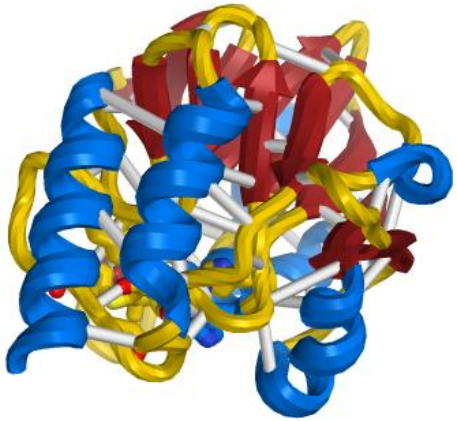
1) Carbapenem: **Meropenem**-resistant strains

Multidrug-resistant penicillin/cephalosporin-resistant carbapenemase-expressing strain eg.

NDM-1 and ideally VIM-1 or their close variants
Meropenem MICs ≥64 µg/ml will be expected and ideally ≥128 µg/ml



Meropenem



3D-Meropenem bound to NDM-1

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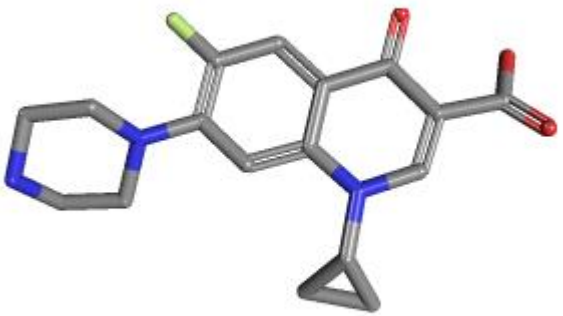
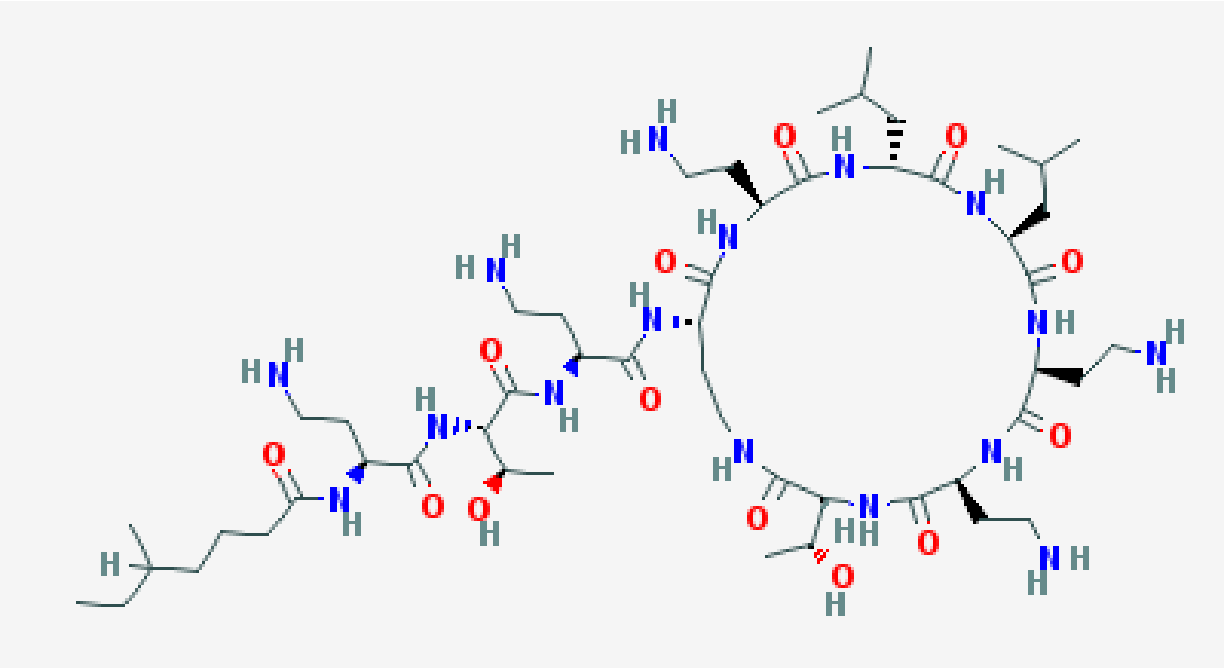
2) Fluoroquinolone: **Ciprofloxacin**-resistant strains

Multidrug-resistant strain, likely to carry defined quadruple GyrA/ParC target point mutations, upregulated expression of efflux pumps and a qnr mutation as well as plasmid based resistance. MIC for ciprofloxacin ≥32 µg/ml.



3) Polymixin: **Colistin**-resistant strains

Multidrug-resistant strains with high level Colistin resistance . Strains will express MCR-1 colistin resistance. Anticipated colistin MIC ≥16 μg/ml.



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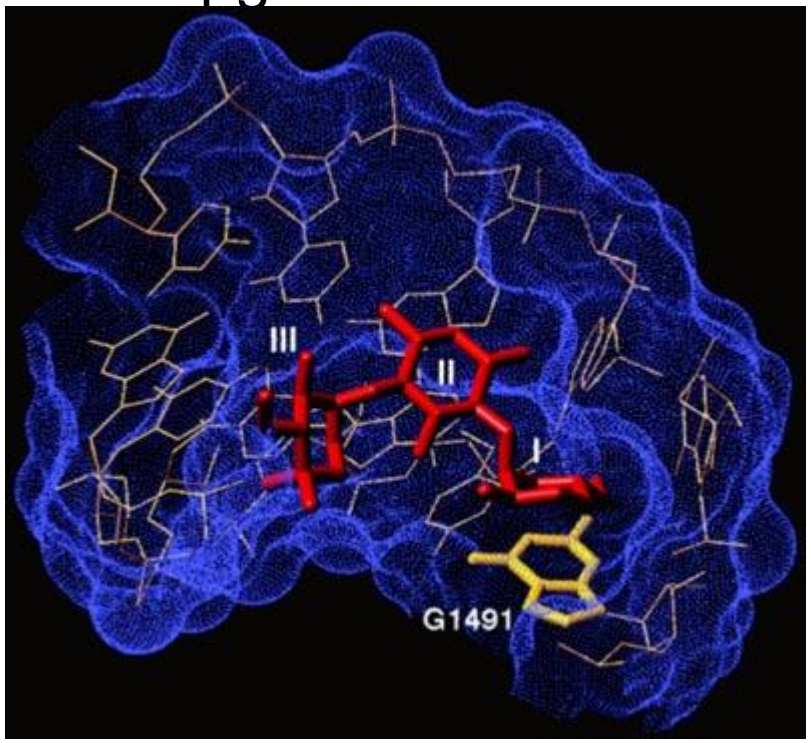
4) Aminoglycoside: **Gentamicin**-resistant strains

Multi-drug resistant strains including a variety of aminoglycoside resistance mechanisms e.g. aminoglycoside modifying enzymes and 16s methyltransferases. Anticipated gentamicin MIC ≥16 µg/ml.



Gentamycin binding to RNA target

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SUMMARY OF ANTRUK's RESEARCH PROGRAMMES

1. Primary screen... full characterisation of interesting ARB combinations
   - as described in previous slides

2. Dose-response / checkerboard combination analysis
   - In vitro microbiological characterization, comparison and prioritisation of the top ARB/antibiotic/pathogen combinations, including 'ideas-led' ARBs selected by literature search (antibiotics and non-antibiotics as ARBs).

3. Characterisation of ARB/antibiotic fixed combinations against clinical isolates
   - The best combinations will be tested against panels of 10 - 20 carefully selected clinical isolates per species.
   - The concentration of ARB required to fully-resensitise the strain to the antibiotic will be determined.

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