Medicine as currently practised throughout the world is threatened by the rise of antibiotic resistant infections. In 2014 it was reported that 50,000 people a year die from antibiotic resistant infections in the USA and Europe. Worldwide there may be as many as 700,000 deaths a year. Jim O’Neill, the eminent economist appointed by the Prime Minister as chair of the Government Review of Antimicrobial resistance recently stated “For doctors and for those who have experienced first-hand the anxiety of an infection that is drug-resistant, as a patient or when caring for a loved one, there is little need to prove the importance of tackling antimicrobial resistance.”1,2 The Prime Minister stated in 2014 that the world could soon be “cast back into the dark ages of medicine” unless action is taken to tackle the growing threat of resistance to antibiotics”3.

Similar views have been expressed by The World Health Organisation4, the President of the United States5, the UK Chief Medical Officer6 and many others. Bacteria are fast becoming resistant to antibiotics and there has been a dearth of new antibiotics discovered during the past 30 years as the figure shows. A major reason for the lack of new antibiotics stems from the closing down of antibiotic research programmes by the large pharmaceutical companies who are unable to make a financial return on antibiotic drugs (see Figure 1).

It is easy to forget what a world without antibiotics looks like. Ordinary surgery becomes more risky and medical interventions ranging from surgeries requiring immunosuppression to simple wound treatments would be compromised or even impossible without antibiotics. Mortality in childbirth and diseases such as meningitis and pneumonia would increase dramatically. The rise of antibiotic resistance could mean that we go back again to this ‘pre-antibiotic era’.

Concerned by the lack of progress in antibiotic development a network of eminent UK scientists came together to discuss what could be done. Arising from these discussions charity Antibiotic Research UK – developing the ‘discovery void’

Figure 1. Dates for antibiotic discovery and the ‘discovery void’

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Colin Garner
(Chief Executive, Antibiotic Research UK)

and David Brown
(Chair, Antibiotic Research
UK Science and Technical Advisory Committee)

ANTRUK is a national charity dedicated to finding new antibiotics against resistant bacteria. It aims to raise money primarily in the UK and is seeking support from Foundations, Trusts, Industry and the general public. The Charity is a Charitable Incorporated Organisation (CIO) and is able to act as a not for profit company.
Target Product Profile

ANTRIUK has prepared a Target Product Profile (TPP) for the molecules to be first screened in vitro.

General criteria for selection of an Antibiotic Resistance Breaker (ARB)

Each of the three products is a molecule to be co-administered with an antibiotic, to break resistance. Molecules will be selected from currently approved and available (non-antibiotic) drugs, nutraceuticals or pure active ingredients of foodstuffs acknowledged as satisfying internationally-agreed GRAS (Generally Regarded as Safe) standards, to allow rapid, safe and low-risk development.

Molecules will be selected that, in the laboratory, have different profiles of effects in breaking resistance: we aim to select a different one for three of the major antibiotic classes used against Gram-negative bacteria.

Preclinical criteria

Three different ARBs will be selected based on the following criteria:

- from different chemical classes
- break resistance to at least one antibiotic class mediated by one or more genetic mechanisms in several or all of the four targeted multidrug resistant Gram-negative bacterial species
- low propensity for rapid emergence of bacterial resistance
- intravenous dosing in humans is possible (potency, solubility, safety, excretion)
- concentrations required for ARB activity are no higher than the plasma range achieved by the molecule in current use
- co-administration in vivo of the ARB with the partner antibiotic is possible
- co-formulation with the partner antibiotic is achievable
- pharmacokinetic properties of the combination are acceptable
- safety of the combination is acceptable
- low cost of goods, affordable globally

Clinical criteria

Indication:

- Primary indication: combination therapy for treatment of life-threatening infection by Gram-negative bacteria requiring hospitalisation
- Secondary indication: potential to be developed for oral therapy

Route of administration:

- Primary: intravenous, for use in hospitals
- Secondary: oral, for hospital and GP use

Dose form:

- Fixed dose combination
- Primary: single formulation for intravenous dosing
- Available as a pre-formulated solution or as dry powder to be rehydrated
- Secondary: single tablet for oral administration, total dose under 1 gram
- Intravenous form storage minimum stability 6 months. Oral dose form storage minimum 2 years
- Heat stable

Dose frequency:

- Primary: intravenous, QD
- Secondary: oral, 1-3 times daily

Efficacy:

- Antibiotic resistance is reduced or eliminated allowing renewed use of antibiotic at approved therapeutic dose level and dosing schedule.

Safety:

- No safety issues added incremental to those of the original antibiotic.
- Suitable for use in all age groups, infant, child, adult.
- No abuse potential.

References