Spotlight on Antibiotic Research UK

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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.” 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.

Similar views have been expressed by The World Health Organisation, the President of the United States, the UK Chief Medical Officer 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 new antibiotics (ANTRUK) was formed to fund novel approaches to antibiotic development. The charity’s initial target is to raise £30m in the next 5–7 years with the aim of developing one new antibiotic therapy by 2020 with further development a network of eminent UK scientists came together to discuss what could be done. Arising from these discussions charity Antibiotic Research UK – developing new antibiotics (ANTRUK) was formed to fund novel approaches to antibiotic development. The charity’s initial target is to raise £30m in the next 5–7 years with the aim of developing one new antibiotic therapy by 2020 with further development of new classes of antibiotic.

The research programmes will be undertaken by a network of leading scientists and clinicians in UK universities and specialty pharmaceutical companies within their existing laboratories and organisations. This network will bring together intellectual insights and development abilities of exceptional quality and at a lower cost than hitherto available. Members of the network are drawn from the following universities: Aston, Birmingham, Bristol, Cambridge, Kings College London, Leeds, Manchester, Newcastle, Nottingham, Oxford, Southampton, St Georges London, Strathclyde, Warwick and York. While these pharmaceutical companies and organisations are also involved in the network: Chemical Biology Ventures, Euprotec, Evotech, Garner Consulting, John Innes Research Centre, Novacta Biosysystems, P A Consulting, Pharmabioquintet, Redex Pharma, Sealife Pharma, Selcia and Transcrip Partners.

The Scientific and Technical Committee (STAC) has determined that the initial research programmes will focus on Antibiotic Resistance Breakers (ARBs). ARBs are molecules that when combined with an antibiotic overcome antibiotic resistance. ARB candidate drugs should be capable of overcoming the diverse mechanisms of resistance that have appeared to our major antibiotic classes. We will select three ARBs from current approved non-antibiotic drugs as a result clinical development can be much more rapid and lower risk than use of totally new molecules. ARBs could be drawn from (a) existing therapeutics from all disease areas (b) nutraceuticals and (c) new chemical entities. ARBs to be screened will be targeted at four Gram-negative antibiotic resistant bacteria – *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumonia*. These four species account for a high percentage of all hospital acquired infections and are the ones the Charity is most keen to tackle early on. The concept of ARBs is not novel; a number of marketed drugs consist of an antibiotic plus another drug such as a β-lactamase inhibitor e.g. Clavulanic acid or clavulanate, usually combined with amoxicillin (Augmentin) or ticarcillin (Timentin), and Sulbactam, usually combined with ampicillin (Unasyn) or Cefoperazone (Sulperazon). A review on ARBs will shortly be published.

It is intended ultimately the whole pharmacoepoeia library will be screened (1000 to 4000 drugs) before examining New Chemical Entities (NCEs).

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.

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

ANTRUK 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