Portcullis House, 24 October 2016

Our research programs: Current status and plans over the next 2-3 years

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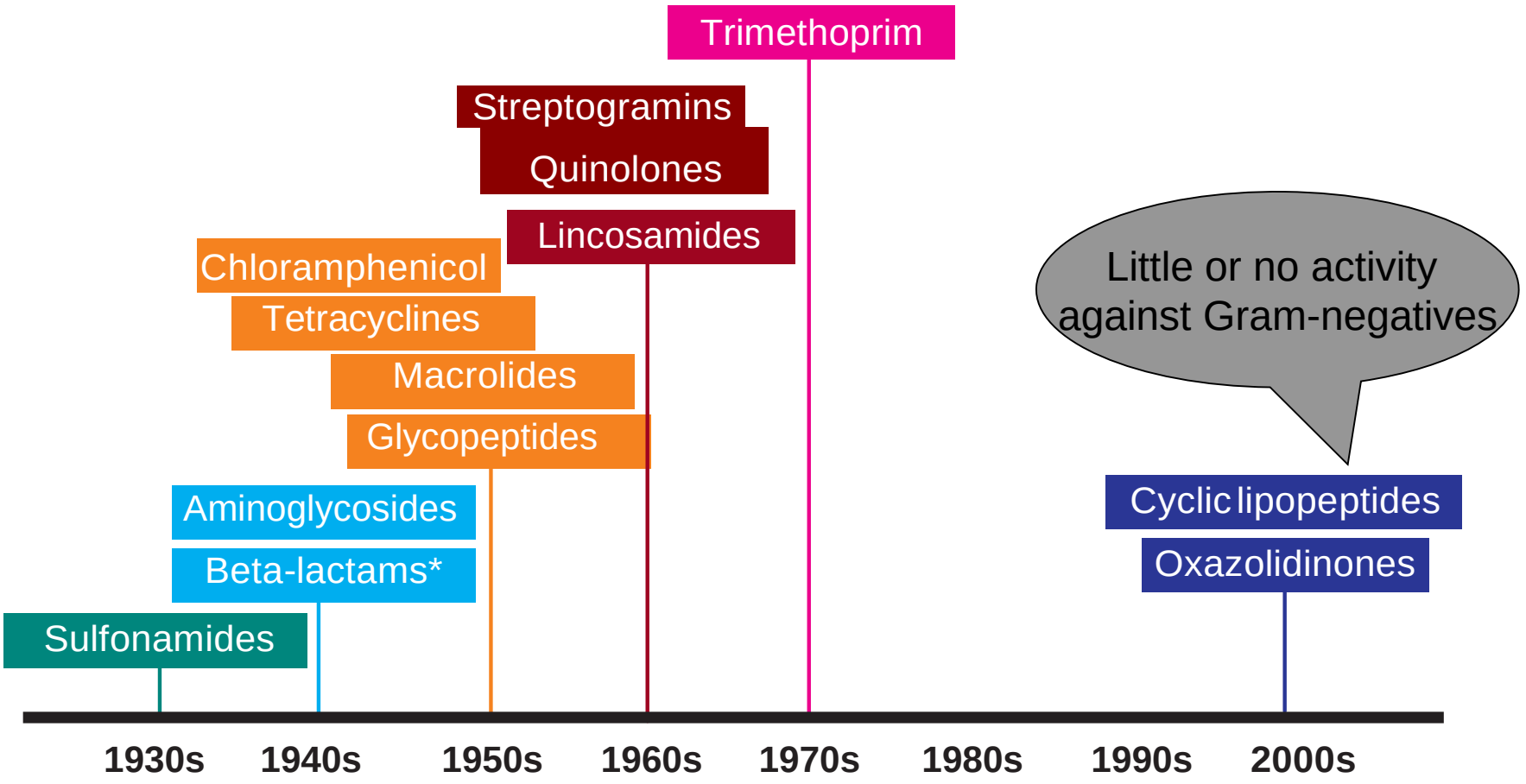
Focus initially on antibiotics against Gram-negative bacteria.
No new chemical classes since 1970s.



World Health Organization

Antibiotic RESEARCH UK

3 Phases of Research at Antibiotic Research UK

1. **2016 (studies in progress, results 1Q2017)**

   Repurposed non-antibiotic drugs as ARBs to break resistance, to save some key antibiotics

   - additional studies to confirm most promising findings during 2017

   - higher levels of funding will be required to progress towards clinical trials in 2018-19

2. **2017 (results 3Q2017)**

   Combinations of 2 or more antibiotics to break resistance

   - additional studies to confirm most promising findings during 2017-8

   - higher levels of funding will be required to progress towards clinical trials in 2019-20

3. **2018? (Depends on funding availability)**

   Develop existing unexploited chemical templates with antibiotic and ARB potential (parked by pharmaceutical companies for 'lack of commercial return')

Antibiotic RESEARCH UK

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.

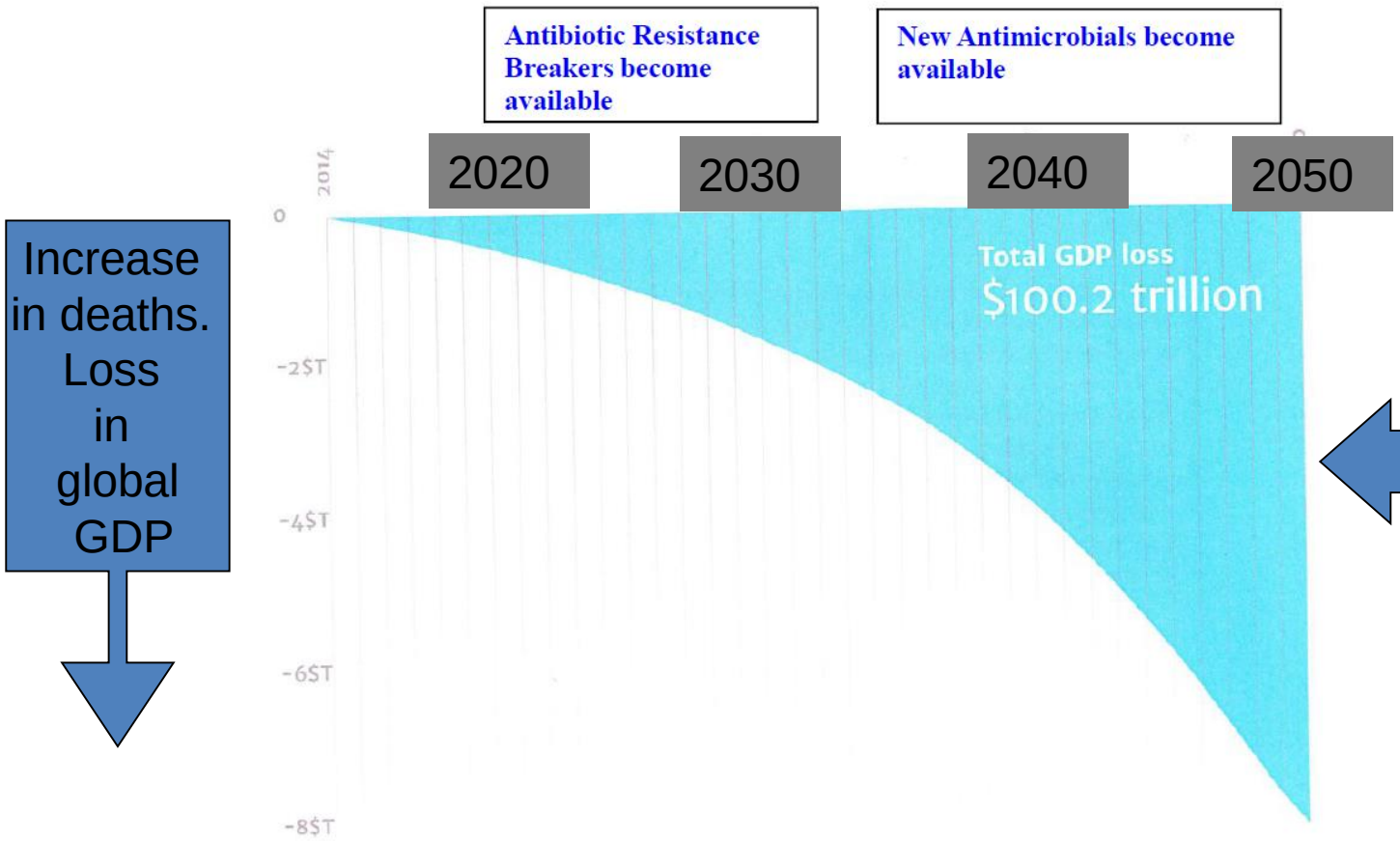
- We need alternative approaches to breaking resistance.

- Growing evidence that several non-antibiotic drugs can be dosed alongside antibiotics to 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 deepen the science base to support evidence-based use in hospitals.

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

Antibiotic RESEARCH UK

Some 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 further investigation.

Resistance to current antibiotics is rapidly increasing. In its 2014 report of global antimicrobial resistance, the World Health Organization (WHO) portrayed high levels of antibiotic resistance in the bacteria that cause common infections. A number of leading authorities have issued passionate statements urging action, including the owing to their role in many infections in human organs (such as the lung and urinary tract), the frequency of antibiotic resistance amongst them and the lack of alternative antibiotics[1]. Several of these pathogens are Gram-negative bacteria, which are of particular concern as in these organisms resistance of up to 50% against carbapenems, 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 available penicillins, cephalosporins and β-lactamase inhibitors, including clavulanic acid and avibactam (FIG. 1). These bacteria are also resistant to virtually all other antibiotics, with the exception of colistin, an old (and somewhat toxic) polymixin class antibiotic, although even colistin resistance has now emerged in South Asia. Both KPC and NDM, as well as Verona integron-encoded metallo-β-lactamase (VIM), have been

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

Our 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

Antibiotic RESEARCH UK

Contract studies currently in progress

Lab work contracted to Evotec Ltd (Manchester/Toulouse). June 2016 to 1Q2017

1. **2016 (studies in progress, results 1Q2017)**

   Repurposed non-antibiotic drugs as ARBs to break resistance, to save some key antibiotics

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Lab work contracted to LGC Ltd (Newmarket). October 2016 start.

2. **4Q2016 - 2017**

   Combinations of 2 or more antibiotics to break resistance

   - additional studies to confirm most promising findings during 2017-8

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3. **2018? (Depends on funding availability)**

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Antibiotic RESEARCH UK

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

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DEVELOPING NEW ANTIBIOTICS