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Department
of Health

What if there are no new antibiotics?

Highlights of a Wellcome Trust & Department of Health (England)
initiated & sponsored
review & report
into

“Alternatives to Antibiotics”

STOA EuCheMS

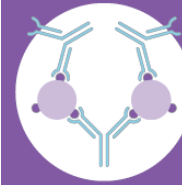
28 April 2016

European Parliament, Brussels

Dr Lloyd Czaplewski FRSC

Alternatives to Antibiotics (A2As)

- Review scope
 - Non-compound approaches that target bacteria
 - Approaches that target the host
 - Suitable to treat systemic or invasive infection
 - Administered intravenously, orally or by inhalation
 - Mono-therapy, combination therapy and/or prophylactic use
 - External topical administration excluded
- Formation of a Working Group to consider and to provide a consensus on A2As to inform development of policy in the AMR area



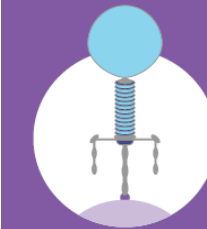
Antibodies

Bind to particular bacteria or their products, restricting their ability to cause disease



Probiotics

Prevent pathogenic bacteria colonising the gut



Lysins

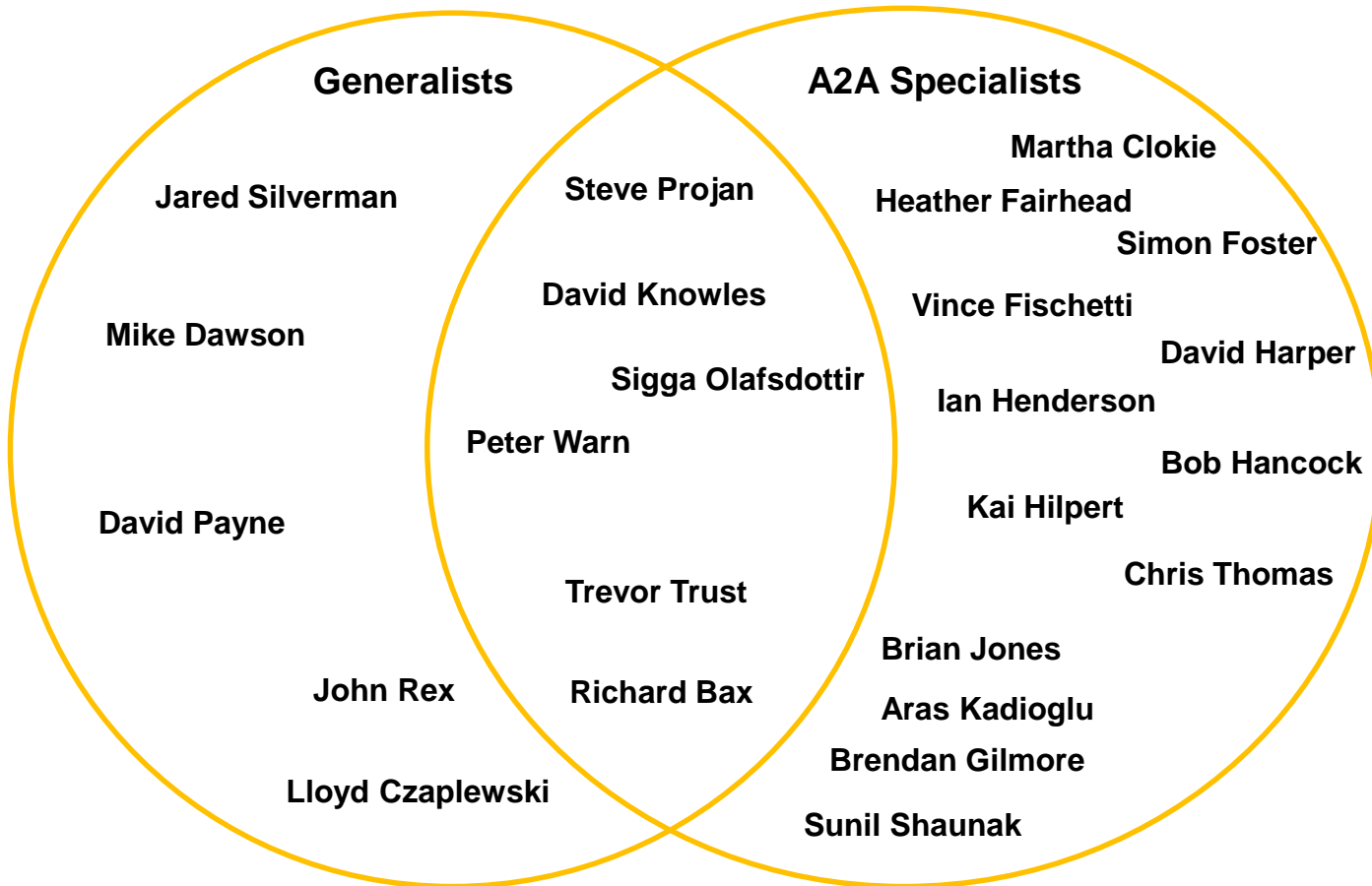
Enzymes that directly and quickly act on bacteria



Peptides

Non-mammalian animals' natural defences against infection

The Working Group (24)



Review process

- 50-page technical report on 19 A2A approaches
- Meeting at the Wellcome Trust 10 December 2014
- Collective email “debate” & iterative maturation of the technical report
- Transformation of the report into a consensus Lancet ID manuscript
- Publication of the review in Lancet ID online Jan 12 2016

Alternatives to antibiotics—a pipeline portfolio review

Lloyd Czaplewski, Richard Bax, Martha Clokie, Mike Dawson, Heather Fairhead, Vincent A Fischetti, Simon Foster, Brendan F Gilmore, Robert EW Hancock, David Harper, Ian R Henderson, Kai Hilpert, Brian V Jones, Aras Kadioglu, David Knowles, Sigríður Ólafsdóttir, David Payne, Steve Projan, Sunil Shaunak, Jared Silverman, Christopher M Thomas, Trevor J Trust, Peter Warn, John H Rex

Lancet Infectious Diseases Volume 16, No. 2, p239–251, February 2016

A2A Review/Lancet ID Article Impact

- O'Neill AMR Team
 - Article informed the Vaccine & Alternatives report (11th Feb 2016)
 - A2A's to be treated **on par with antibiotics** with access to the proposed Global Innovation Fund



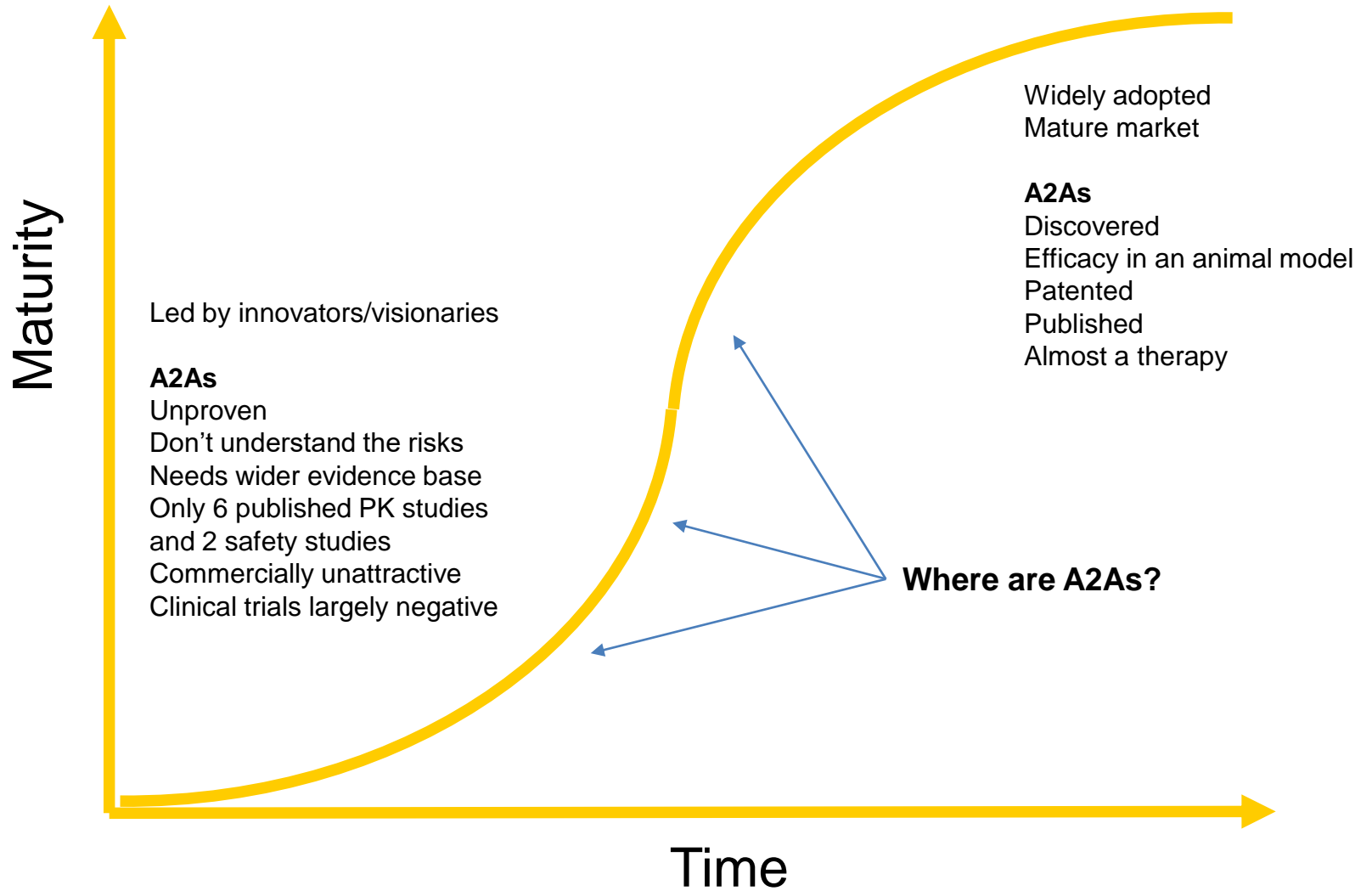
World Health
Organization

DNDi/GARD

- Elsevier Atlas Award for research impact



Alternatives to Antibiotics



Given the current A2A portfolio we cannot expect a new *therapeutic* to treat systemic or invasive bacterial infection within the next 10 years

Approach	Probability of registration by 2025 %	First in man use	Target bacteria
Antibodies	170	Prevent	<i>P. aeruginosa, S. aureus, C. difficile</i>
Probiotics	124	Treat or Prevent	<i>C. difficile</i>
Lysins	26	Treat	Gram-positive & Gram-negative?
Bacteriophages	9	Treat	<i>P. aeruginosa, C. difficile</i>
Immune Stimulation	43	Prevent or Adjunct	<i>C. difficile, Broad-spectrum</i>
Vaccines	188	Prevent	<i>C. difficile, P. aeruginosa, S. aureus</i>
Peptides	<20	Treat or Adjunct	<i>P. aeruginosa, C. difficile, S. aureus</i>

With adequate funding into antibodies, probiotics and vaccines, we expect registration of:-

- 2 new medicines for *C. difficile* (probiotic and antibody or vaccine) by 2019
- 1 for *P. aeruginosa* (antibody or vaccine) by 2021
- 1 for *S. aureus* (antibody or vaccine) by 2022

The A2A experiment

- Antibiotics have provided multiple medicines over 70 years & a huge investment
- A2As have not had the same investment
- Insufficient experience and literature of preclinical to clinical transition
- Clinical potential unproven
- Challenging investment argument

- BUT potentially a new source of medicines

- Identify which approaches are most attractive;
- Develop diagnostics to enable use of targeted therapies
- Refocus healthcare from treatment to prophylaxis
- Multiple products will be required to replace a single antibiotic
- Funding should focus on market pull rather than research push
- Invest in experimental clinical medicine not just drug discovery
- Develop A2A networks and a more collegiate approach
- Without adequate funding we cannot act as if there will be replacements for antibiotics

Opportunity – just not enough activity?

Alternatives to Antibiotics

£1.5 bn
€1.9 bn



- Antibodies
- Probiotics
- Lysins
- Bacteriophage
- Immune stimulation
- Vaccines
- Peptides
- Immune suppression
- Anti-resistance nucleic acids
- Antibacterial nucleic acids
- Toxin sequestration
- Antibiotic-degrading enzymes
- Transcriptional regulation
- Alphaners
- Metal chelation
- Apheresis of protective antibodies

Approaches

>£10 bn
>€13 bn



- Natural products
- Alternatives to antibiotics
- Next Gen Scaffolds
- Novel compounds vs known targets
- Combinations of antibiotics
- Efflux Pump Inhibitors
- Resistance breakers
- Novel targets & compounds

Solving the problem of antibiotic resistance

- Partnerships
 - experience, skills and insights
- International
- Coordinated
- Sustained
- Generational challenge
- Big science budgets

>£10 bn

>€13 bn



LHC £6 bn

€8 bn



ISS £96 bn

€123 bn