



Innovative Medicines Initiative

Combating Antibiotic Resistance: New Drugs 4 Bad Bugs (ND4BB)

David Payne/Seamus O'Brien for Astra Zeneca,
Basilea, GlaxoSmithKline, J&J & Sanofi



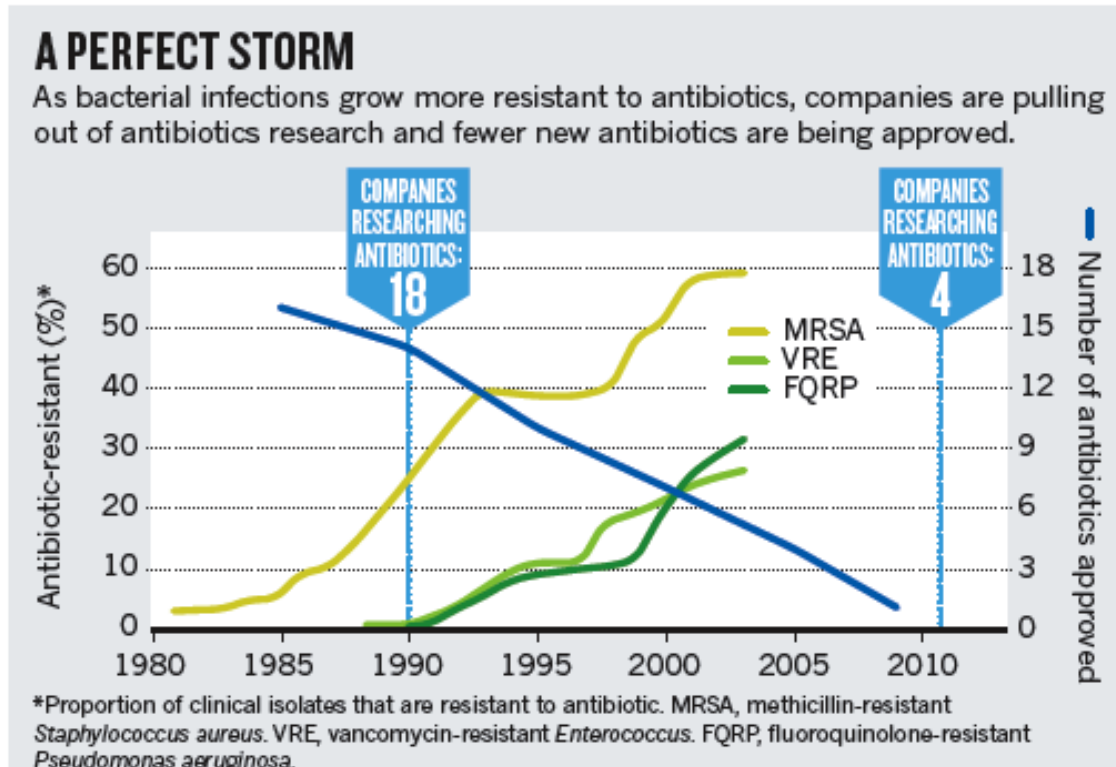
efpia

Need for public-private collaboration



Challenges of AB R&D:

1. Unique scientific bottlenecks
2. Challenging regulatory environment
3. Low return on investment



32 | NATURE | VOL 472 | 7 APRIL 2011

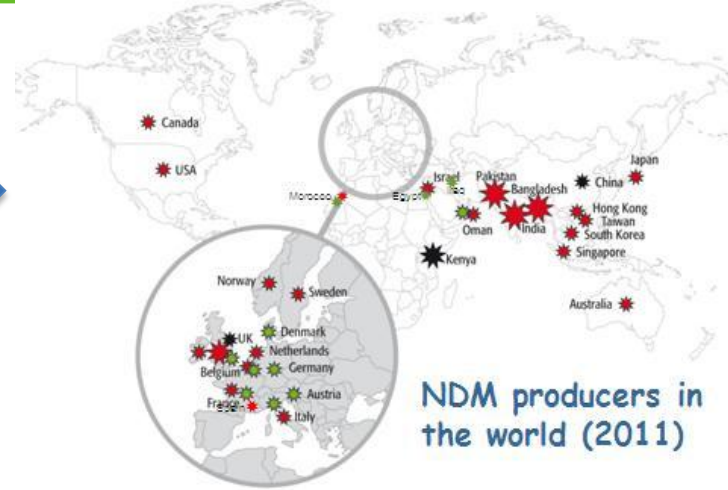
Challenges too great for any single entity to solve, collaboration is essential



Antimicrobial resistance is unpredictable



Environmental sites of NDM-1 producers (Delhi)



NDM producers in the world (2011)

STAR SIZE
 * 1-5 cases * 6-50 cases * > 50 cases
 Nordmann P, Nass T, Poirel L. *Emerg Infect Dis.*

- NDM spread to ICUs across Europe in <18 months
- Numerous examples of rapid global spread of clones & resistances
- Takes 10+ years to make an AB
- Long term strategy needed for threats of today and the future

Spain ^{23F} – 1 Pneumococcal Clone



Nordmann et al (2011); *Emerging Infect Dis* 17; 1791-8.
 Klugman (2002); *J. Antimicrob Chemother*, 50; S2, 1-5.
 Walsh et al (2011); *Lancet*, 11,(5), 355- 362



Objectives of the full project



- Response to the European Strategy to combat antibiotic resistance
 - AB R&D PPPs have been the subject of years discussion; ND4BB establishes Europe as a leader in addressing AMR
- Information sharing amongst collaborators in a way we have never done before
 - Need to increase the overall success of AB R&D, as an industry we cannot afford to make the same mistakes twice
- Projects focused on the treatment/prevention/management of resistant infections caused by:
 - Drug-resistant Gram-negative pathogens
 - *Clostridium difficile*, MRSA



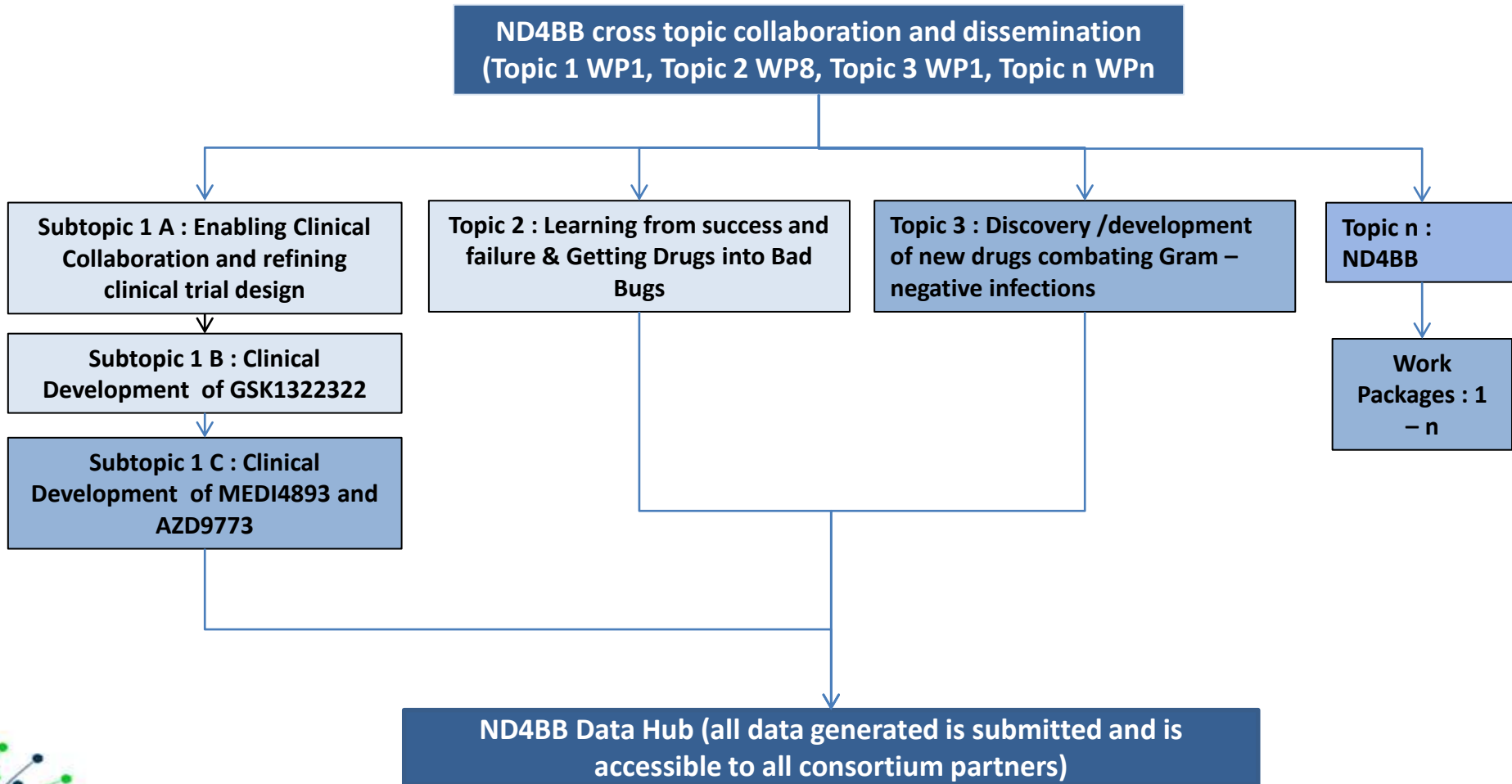
Expected impact on the R&D process



- Sharing of successes and failures amongst the industry will increase the efficiency of AB R&D
- Potential to create smaller & more efficient clinical trials
 - Biomarker research and rapid diagnostics could enable targeted patient enrolment
- Creation of a clinical trial consortium for antibacterials
 - Creation of more sites in areas of high resistance
 - Communication of best practice and learnings
- Ability to rationally design compounds that penetrate Gram negatives will facilitate the delivery of a pipeline of AB for Gram negatives



Suggested architecture of the project



-  Topics launched under Call 6
-  Future Topics to be launched



Key deliverables of the full project: Topic 1



- *Challenge being addressed:* funding for AB clinical trials is a major cost of AB development (in some cases prohibitive)
- *Goal & Deliverables:* Provide clinical data on new agents for tackling priority pathogens and improve the efficiency of AB clinical trials
 - Generation of clinical data that demonstrate the efficacy, safety and pharmacology of new agents for priority pathogens
 - Create the first clinical trial consortium for ABs
 - Create opportunities to test diagnostics/biomarkers etc
 - Create new clinical trial sites in regions/institutions of high resistance
 - Innovative Phase 2 and Phase 3 designs



Subtopic 1A : Enabling clinical collaboration & refining clinical trial design



- Key Objectives
 - Facilitate and enable a highly functional, compliant and trained clinical trial investigator network.
 - Ensure cross collaboration between ND4BB projects

- Work Package Outline
 - WP1:Overall communication amongst Topic 1 investigators and ND4BB
 - WP2:Training AB clinical trial investigators for consortium network
 - WP3:Surveillance with new AB agents to assess pre-existing resistance and pinpoint regions/institutions of high resistance
 - WP4:Innovative Phase 2 and 3 design



Subtopic 1B: Innovative trial design & Clinical drug development



- Key Objectives
 - Conduct prospective clinical trials to evaluate safety, pharmacology and efficacy data for GSK1322322.
 - Validate novel bacterial diagnostics or novel biomarkers with the aim of reducing the size and cost of clinical trials.
- Work Package Outline
 - WP5A: 1st Phase 3 GSK1322322 in ABSSSI with oral switch
 - WP5B: 2nd Phase 3 GSK1322322 in ABSSSI with oral switch
 - WP5C: Phase 2IIb: GSK1322322 for hospitalised CABP with oral switch
 - WP5D: GSK1322322: Pivotal Phase 3 trials for hospitalised CABP



ABSSSI: acute bacterial skin and skin structure infections
CABP: Community acquired bacterial pneumonia



efpia

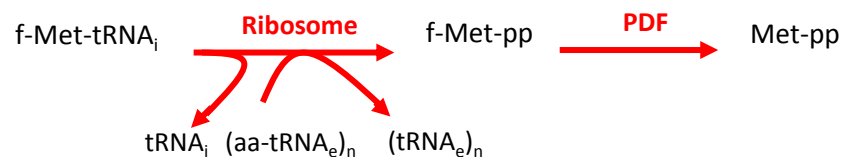
GSK322 Inhibits the PDF Enzyme An Unprecedented Antibacterial Target



Compound Overview

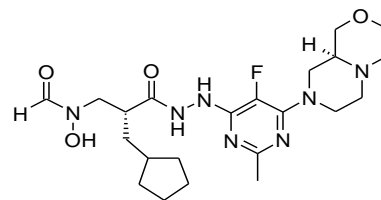
- Entirely novel antibacterial target
- No cross-resistance with currently available antibiotics
- Targeted *in vitro* spectrum against typical and atypical community acquired pneumonia pathogens including MRSA
- IV & oral formulations
- Phase I and IIa completed
- Provisional safety and efficacy data from completed Phase IIa study in ABSSSI (MRSA skin infections)

Peptide Deformylase (PDF)



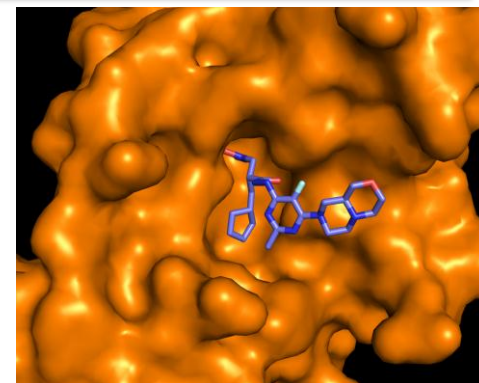
PDF: Removes N-formyl group from newly-synthesized peptides

Structure-based design efforts led to the discovery of '322



GSK1322322

Novel hydrazinopyrimidine
PDF inhibitor series



In vitro activity of GSK1322322

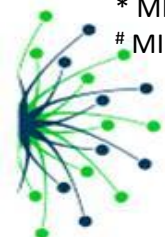


Organism (N)	MIC ₉₀ (µg/mL)			
	GSK1322322	Azithromycin	Clindamycin	Levofloxacin
<i>S. pneumoniae</i> (961)	2	>8	>4	1
Pen ^R <i>S. pneumoniae</i> (402)	1	>8	>4	8
Mac ^R <i>S. pneumoniae</i> (337)	1	>8	>4	8
Levo ^R <i>S. pneumoniae</i> (56)	2	>8	>4	>8
<i>H. influenzae</i> (2553)	4	2	>4	0.03
<i>M. catarrhalis</i> (115)	1	0.06	2	0.06
<i>S. aureus</i>				
MSSA (556)	4	>8	0.25	0.5
MRSA (494)	4	>8	>4	>8
<i>S. pyogenes</i> (653)	0.5	>8	0.06	1
Atypical organisms*				
<i>M. pneumoniae</i>	0.001-0.002	0.002	NT	NT
<i>C. pneumoniae</i>	≤0.25	0.03 - 0.06	>128	0.5-1
<i>L. pneumophila</i> #	2	0.06	NT	0.03

* MICs reported as a range

MIEC (Minimum Extracellular Concentration Inhibiting Intracellular Growth)

Study conducted by IHMA



Subtopic 1C: Innovative trial design & Clinical drug development



Subject to Future Call

- Objectives
 - Create new insights into the epidemiology of surgical site infections in the EU
 - Clinical trials with MED14893 to prevent MRSA infections and AZD 9773 for treating sepsis which is caused by uncontrolled infection
- WP6: Clinical Trials supporting the development of MEDI4893, a monoclonal antibody (mAb) targeting *S.aureus* alpha toxin:
 - WP6A: Epidemiologic surveillance of surgical site Infections (SSI) in the EU
 - WP6B: Evaluate the role of *S. aureus* (inc. MRSA) virulence factors in SSIs
 - WP6C & D: Ph 1b/2 trials for prevention of *S. aureus* (MRSA) VAP and SSIs
- WP7 : Phase 3 AZD9773: Ab targeting tumor necrosis factor alpha for the treatment of the severe sepsis, including septic shock

SSI: surgical site Infections; VAP: ventilator associated pneumonia



Expected contributions of the applicants: Topic 1



- Experts in serious hospitalised bacterial infections to participate in pan-European consortium
- Project Leadership and co-ordination infrastructure
- Hospital and healthcare institutions to join a clinical trial network with capability to run Phase 1, 2 & 3 clinical trials
- SMEs to provide training to ensure a compliant network of clinical trial sites and micro labs
- SMEs with diagnostics suitable for use in clinical trials, experts in novel biomarker research
- Clinical research organisation with global experience
- Expertise in statistics and pre-clinical PK/PD modeling
- Coordination & conducting microbiology surveillance programs



Expected (in kind) contributions of EFPIA members: Topic 1



- Clinical trial expertise
- Knowledge & expertise on GSK1322322, MEDI4893 & AZD9773
 - Provision of study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc.
- Non- Europe component of the clinical trial
- Project/Alliance Management personnel
- Statistics (eg Bayesian), PK/PD modeling & simulation expertise
- Expertise in designing surveillance programmes
- Clinical micro procedures/protocols required in clinical trials



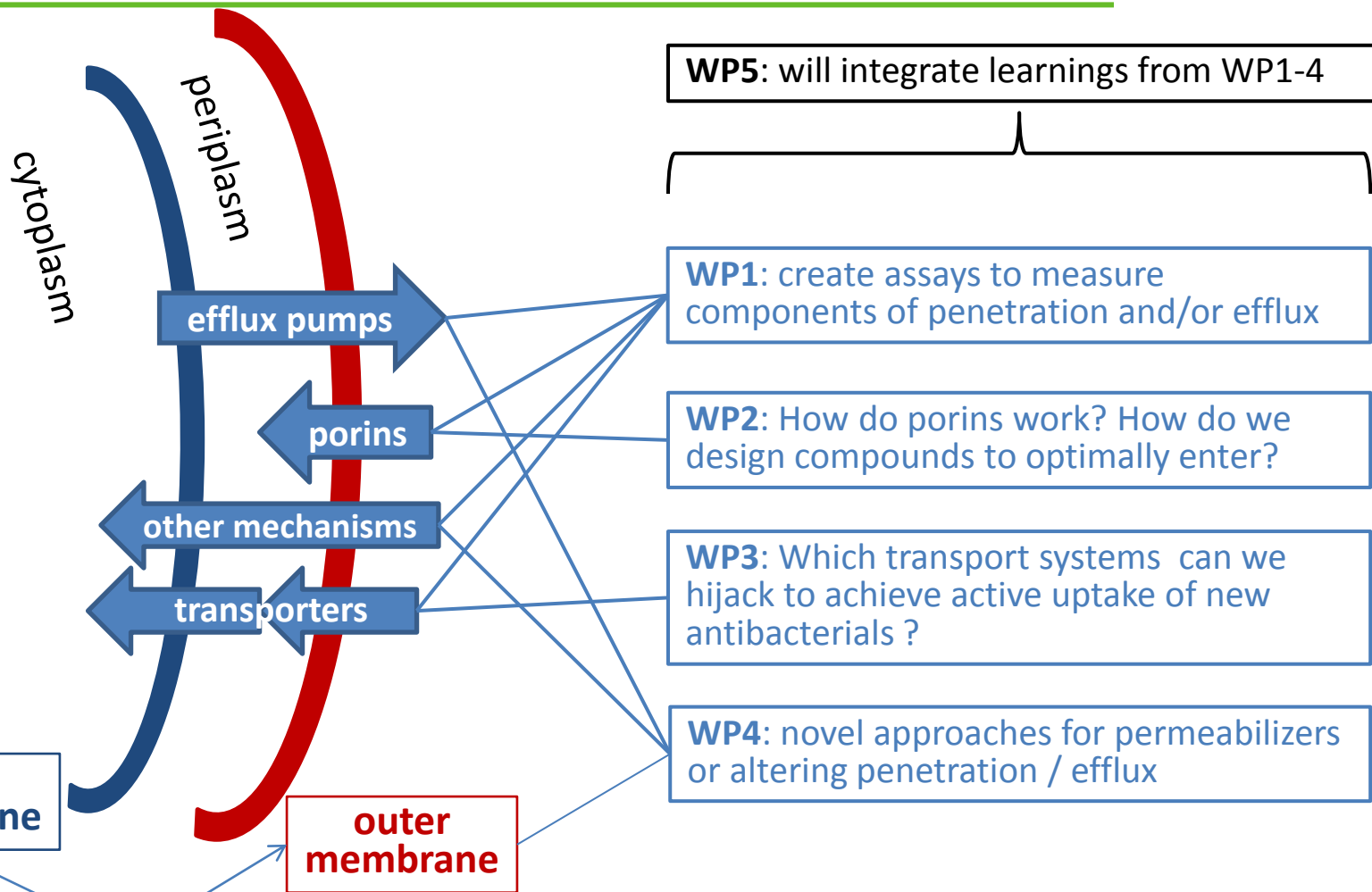
Key deliverables of the full project: Topic 2



- *Challenge:* Making selective inhibitors of novel Gram negative targets is not a substantial challenge – getting them into Gram negatives to reach their lethal target is the bottleneck
 - Industry concludes this is the biggest scientific barrier to the success of Gram negative drug discovery programmes
- *Goal & Deliverables:* Create a partnership with EU academics (inc those new to AB R&D) to enable more rational approaches to design Gram negative AB by enhancing our understanding of how to:
 - Avoid efflux
 - Optimally penetrate porins & Gram negative membranes
 - Hijack active uptake pathways ('Trojan horse' approach)



How will Topic 2 address the penetration challenge?



very different characteristics



Expected contributions of the applicants: Topic 2



WP1-5

- Expertise in measuring cellular penetration and/or efflux (including novel techniques and knowledge transfer from mammalian systems)
- Expertise in studying porin function / SAR
- Expertise in bacterial uptake pathways
- Medicinal chemistry expertise to build in recognition features for uptake pathways into antibacterials
- Techniques to find new targets which alter permeability / efflux

WP6-8

- IT expertise for database infrastructure, web design, etc.
- Scientific communications expertise



Expected (in kind) contributions of EFPIA members: Topic 2



- SAR on novel series of investigational ABs for data mining
 - Supply of lead molecules for building in 'recognition' features for novel uptake pathways
 - Medicinal chemistry expertise specific to the antibacterial therapeutic area
 - Supply of lead molecules for 'mechanism of penetration' experiments
 - Assay development expertise
 - Potential to run HTSs for novel potentiator targets
 - Bacterial strains, tool strains, engineered strains
 - Data visualization and mining expertise, computational and statistical analysis expertise
 - Data on our successes and failures
-



What's in it for you?



- Patients
 - AB resistance threatens our ability to treat common and life threatening infections
 - ND4BB will increase our preparedness to tackle multi-resistant pathogens today and unexpected resistances in the future
- Academic researchers
 - Research opportunities and participation in the 1st AB clinical trial consortium
 - Translation of fundamental science into AB discovery programs
 - Integration & learnings into all aspects of AB R&D
- SMEs
 - Evaluation of promising diagnostics in well controlled trials
 - Training opportunities across Europe to create new clinical trial investigators and compliant sites for AB clinical trials
 - Contract research organisations to work with pharma



Questions?

- Contact the **IMI Executive Office**
 - E-mail: infodesk@imi.europa.eu
 - Website: www.imi.europa.eu
- Links to pages of interest on IMI website
 - Link to call : www.imi.europa.eu/content/6th-call-2012
 - Link to partner search tool : <http://pst.imi.europa.eu/content/imi-pst/en/login.html>
 - Participating in IMI projects : <http://www.imi.europa.eu/content/call-proposals>
- Remember : Final date for submission of expression of interest : 9 July 2012



Backups



AZD9773 : Topic 1C



- **Compound overview**

- AZD9773 is a potential treatment of severe sepsis and septic shock.
- Sepsis arises through the body's response to infection
- There are currently no specific treatments for severe sepsis
- Sepsis is the most common cause of death in the ICU
- Patients with any difficult bacterial infection, both resistant and susceptible, will benefit from access to a treatment for sepsis
- A sepsis treatment would support antibiotic stewardship goals
- AZD9773 is an ovine-derived polyclonal antibody fragment of IgG against human TNF- α .

- **Project Status**

- AZD9773 is currently completing a placebo-controlled Phase 2b study.
- If this study is positive, confirms prior work and suggests that Phase 3 development is appropriate, IMI will release a Call for investigators for this Phase 3 project later during 2012



MEDI4893 : Topic 1C



- **Compound overview**

- *S. aureus* produces tissue and organ damage in part via toxins
- Targeting these toxins preemptively may prevent serious *S. aureus* (including MRSA) disease in high-risk patients, independent of the antimicrobial resistance status.
- MEDI4893 is not expected to contribute to resistance to antibiotics
- MEDI4893 is a potent human IgG1 that binds to *S. aureus* alpha toxin

- **Current Status**

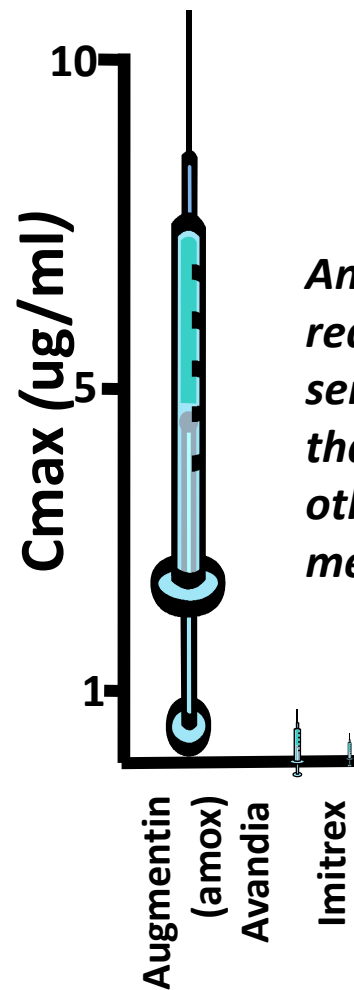
- MEDI4893 is current completing preclinical studies.
- If these studies are successful, MEDI4893 will enter clinical development later this year
- If this occurs, IMI will release a Call for investigators both epidemiologic and clinical studies in support of MEDI4893's initial development



Scientific challenge: Gram negative penetration adds to already daunting set of requirements



- Selective inhibition of target
- Penetration into Gram-negatives*
- Therapeutic window (safety, genotox, QT, etc)
- Suitable PK/PD
- Developable/ Stable Crystalline form
- Scaleable process /viable CoGs



Antibiotics require higher serum levels than many other types of medicines

