Innovative Medicines Initiative

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

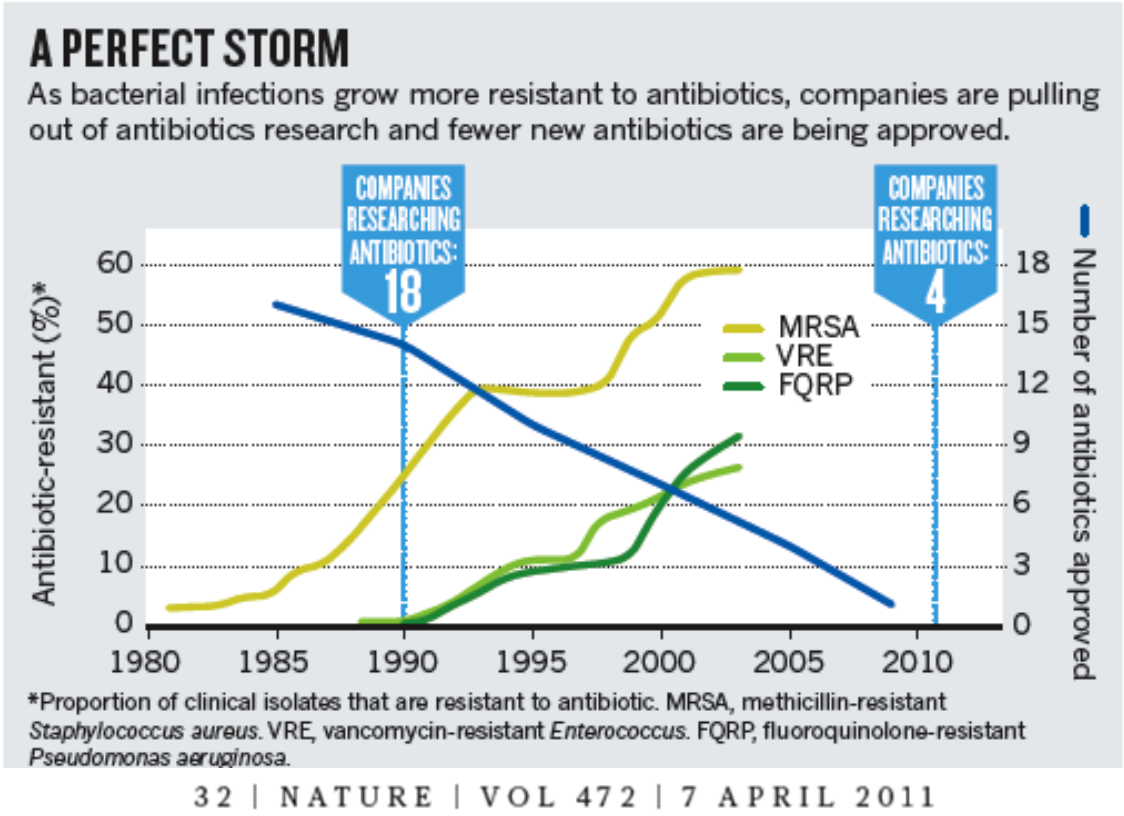
David Payne/Seamus O'Brien for Astra Zeneca, Basilea, GlaxoSmithKline, J&J & Sanofi

efpia

Need for public-private collaboration

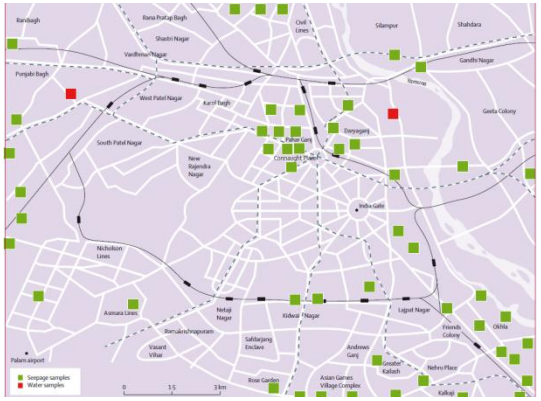
Challenges of AB R&D:

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

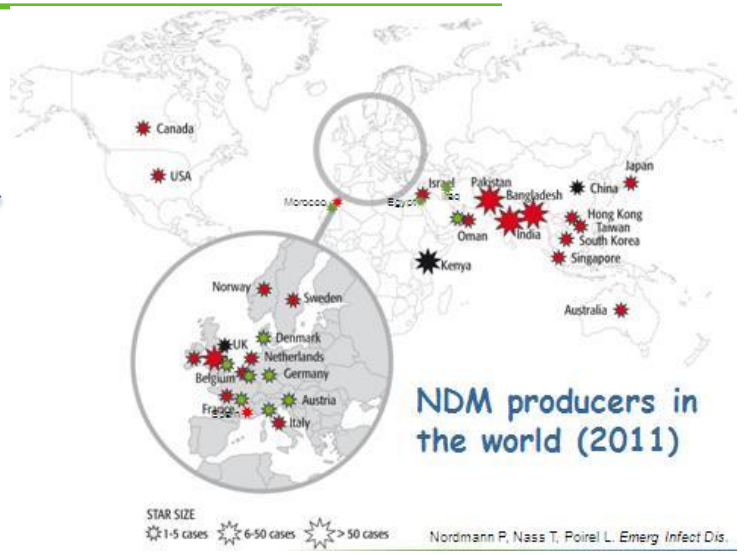


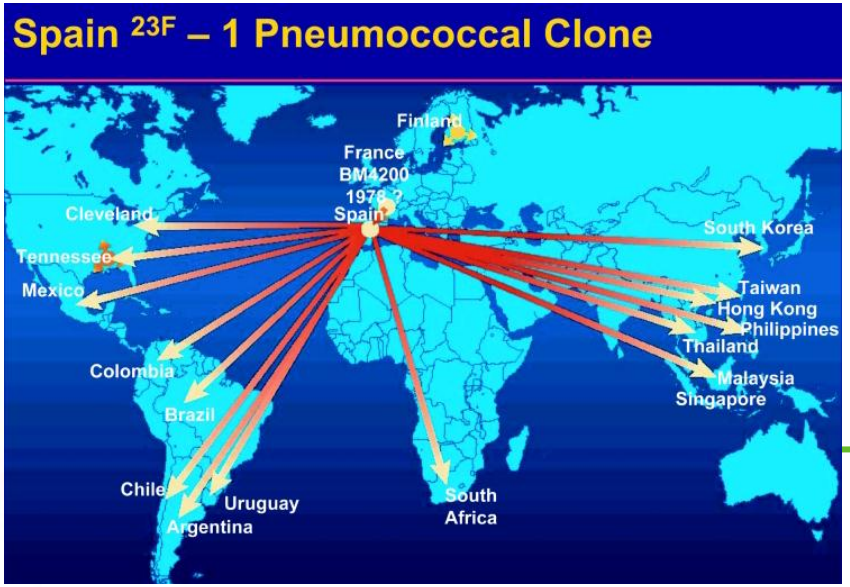
Challenges too great for any single entity to solve, collaboration is essential

Antimicrobial resistance is unpredictable



Environmental sites of NDM-1 producers (Delhi)





- 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

Nordmann et al (2011); Emerging InfectDis 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*

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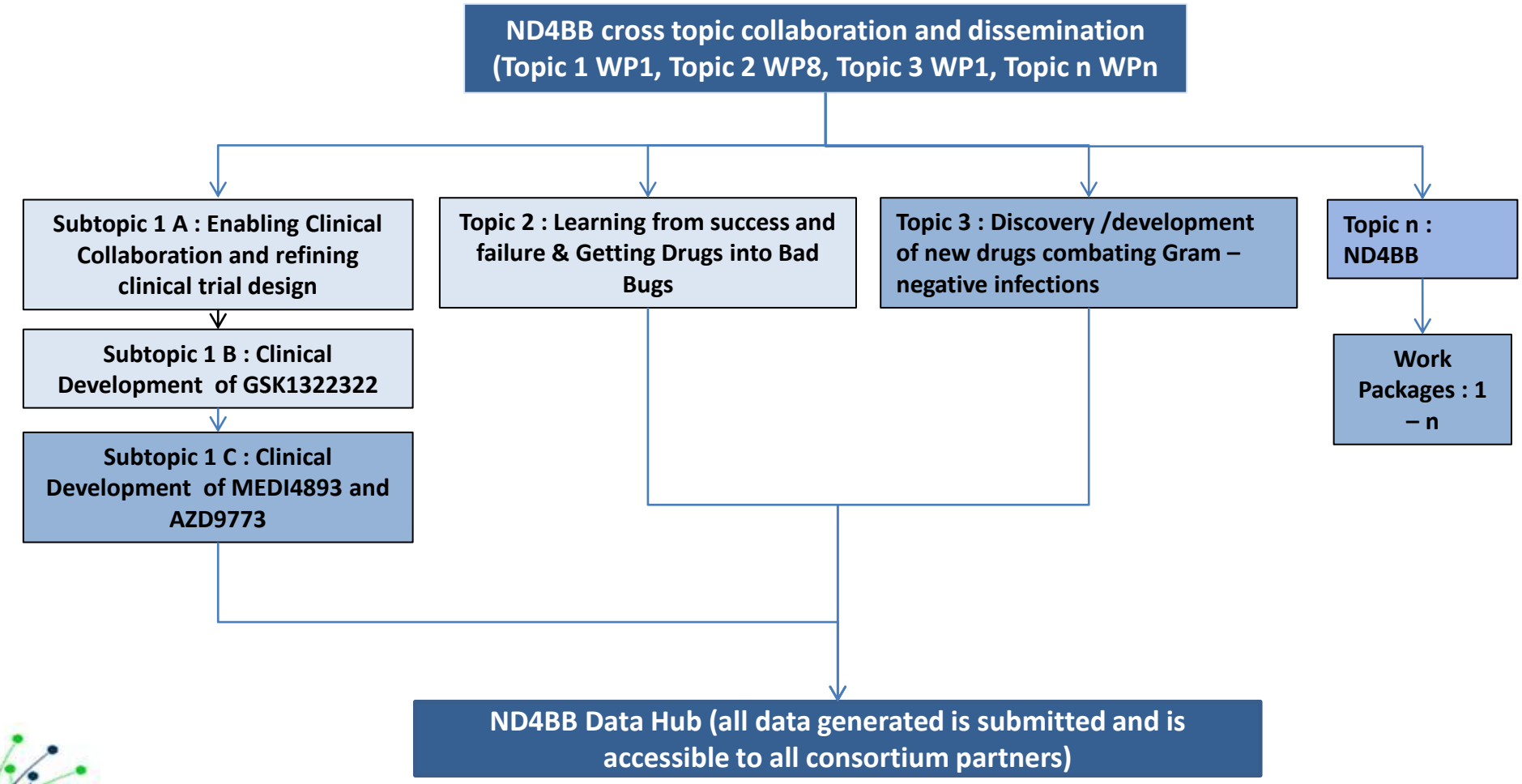
Expected impact on the R&D process

- Sharing of successes and failures amongst the industry will increase the efficiency of AB R&D
- Potential to create smaller & more efficent 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

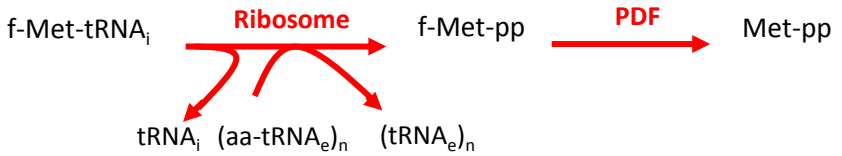
ABSSSI: acute bacterial skin and skin structure infections
CABP: Community acquired bacterial pneumonia

GSK322 Inhibits the PDF Enzyme
An Unprecedented Antibacterial Target

Compound Overview

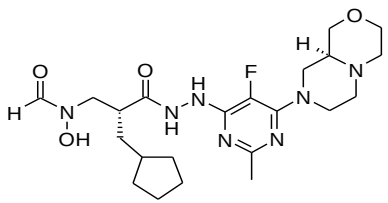
- Entirely novel antibacterial target
- No cross-resistance with currently available antibiotics
- Targeted *in vitro* spectrum against typical and atypical community acquired pneumonia pathogens including MRSA
- IV & oral formulations
- Phase I and IIa completed
- Provisional safety and efficacy data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

Peptide Deformylase (PDF)



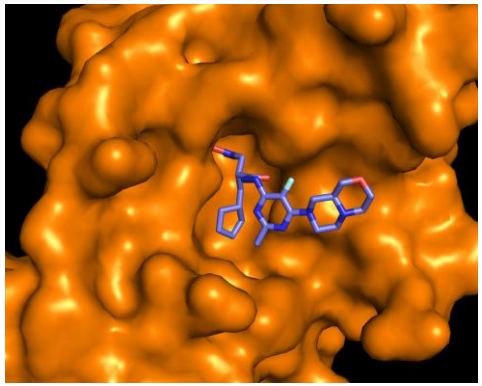
PDF: Removes N-formyl group from newly-synthesized peptides

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
S. pneumoniae (961)	2	>8	>4	1
Pen^R *S. pneumoniae* (402)	1	>8	>4	8
Mac^R *S. pneumoniae* (337)	1	>8	>4	8
Levo^R *S. pneumoniae* (56)	2	>8	>4	>8
H. influenzae (2553)	4	2	>4	0.03
M. catarrhalis (115)	1	0.06	2	0.06
S. aureus				
MSSA (556)	4	>8	0.25	0.5
MRSA (494)	4	>8	>4	>8
S. pyogenes (653)	0.5	>8	0.06	1
Atypical organisms*				
M. pneumoniae	0.001-0.002	0.002	NT	NT
C. pneumoniae	≤0.25	0.03 - 0.06	>128	0.5-1
L. pneumophila #	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

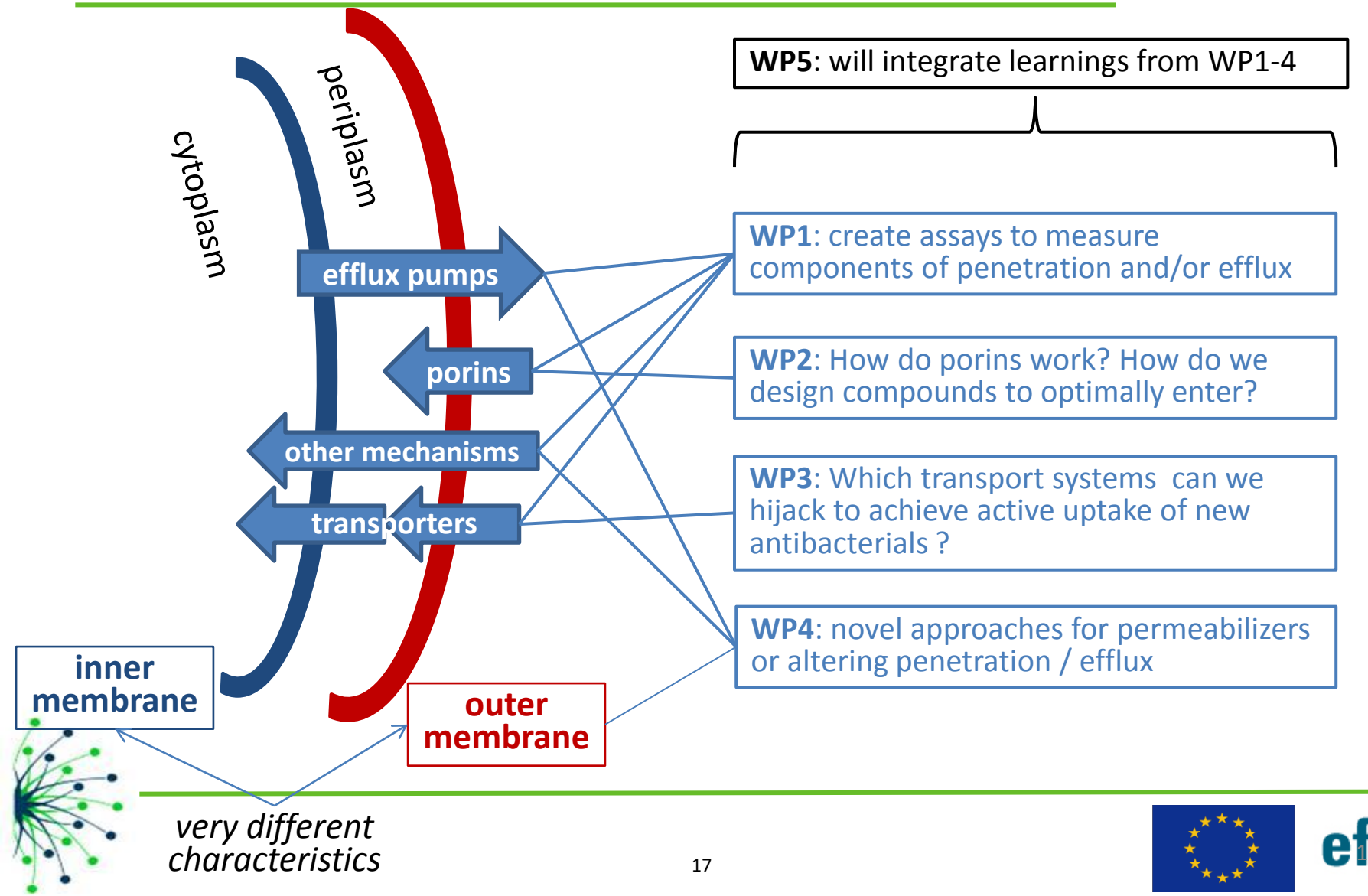
Expected (in kind) contributions of EFPIA members: Topic 1

- 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?



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

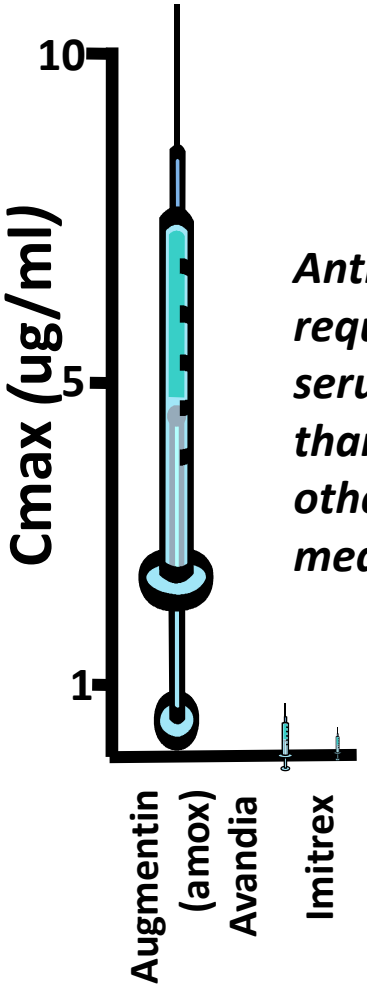
MEDI4893 : Topic 1C

- **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, genetox, QT, etc)
- Suitable PK/PD
- Developable/ Stable Crystalline form
- Scaleable process /viable CoGs



Antibiotics require higher serum levels than many other types of medicines