Innovative Medicines Initiative

New Drugs for Bad Bugs (ND4BB)
Topic 6

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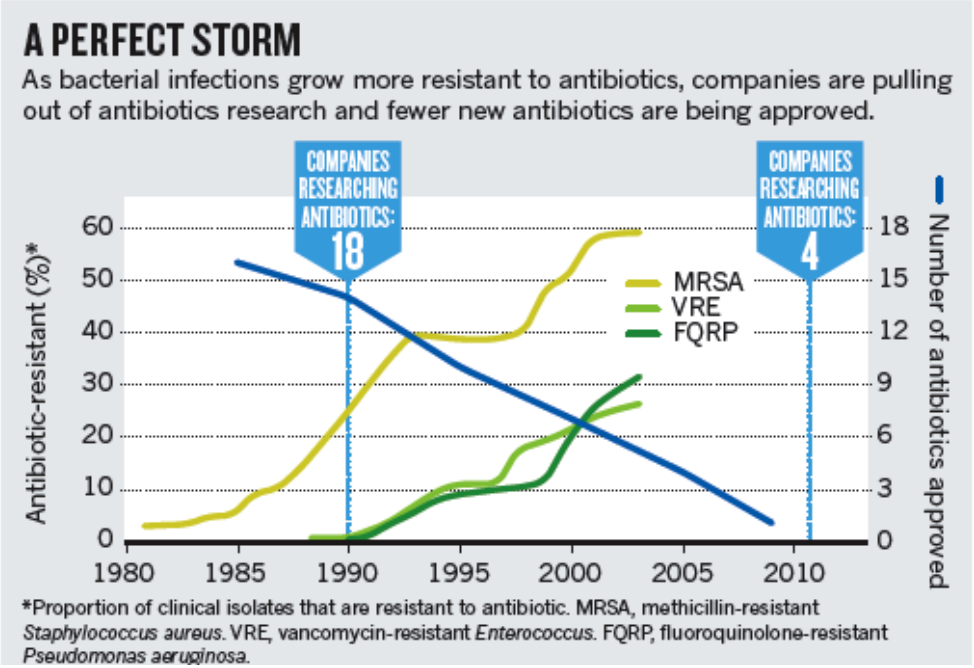
efpia

ND4BB: Need for public-private collaboration

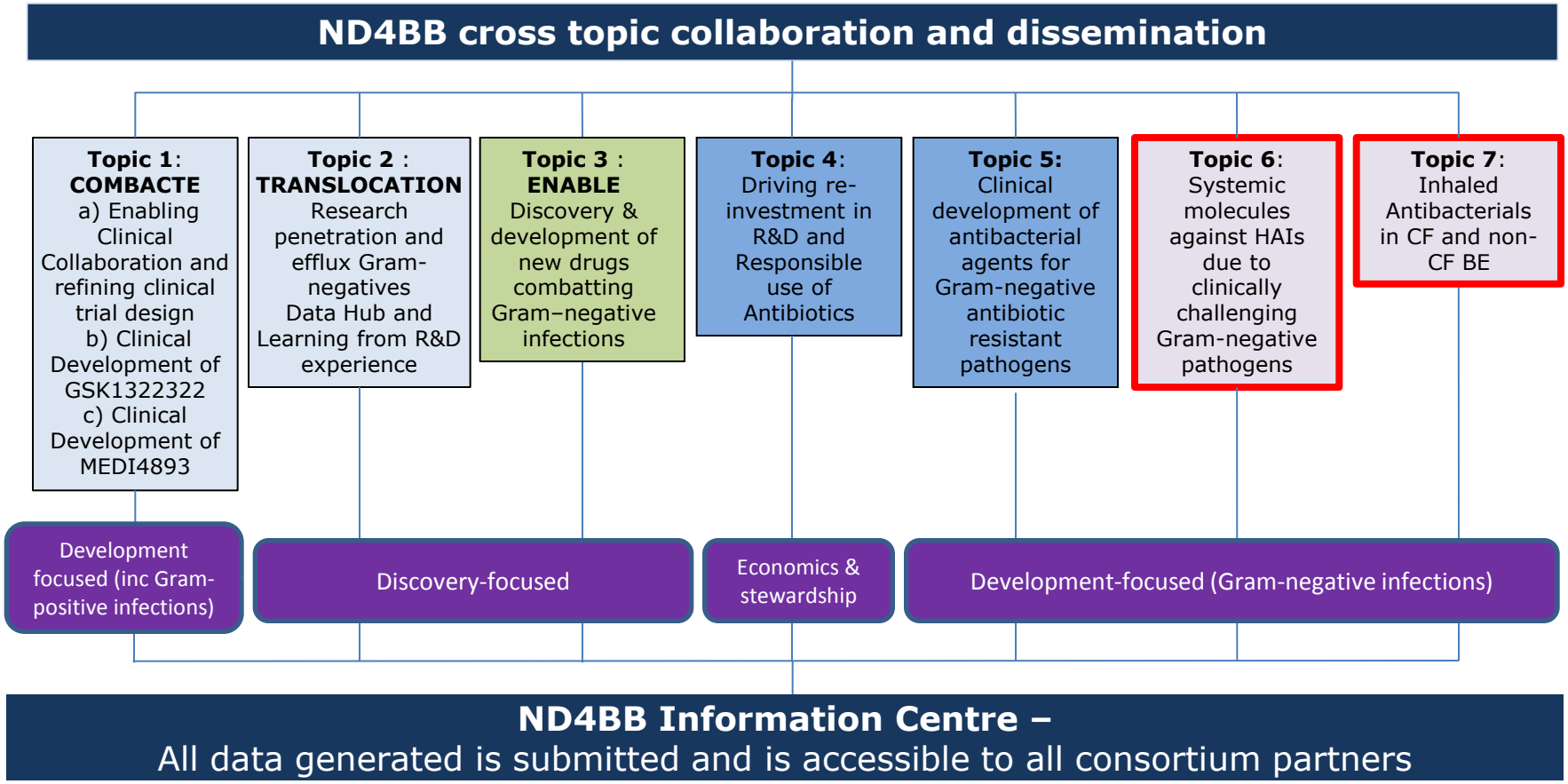
- *The overall vision of ND4BB is to create an innovative collaborative Public-Private Partnership (PPP)-based approach that will encompass all aspects from the discovery of new antibiotics to Phase 2 and 3 clinical trials with the aim of reinvigorating antibiotic R&D*

Three key challenges in antibiotic R&D:

1. **Discovery:** Unique scientific bottlenecks
2. **Development:** Challenging regulatory environment
3. **Economics:** Low return on investment

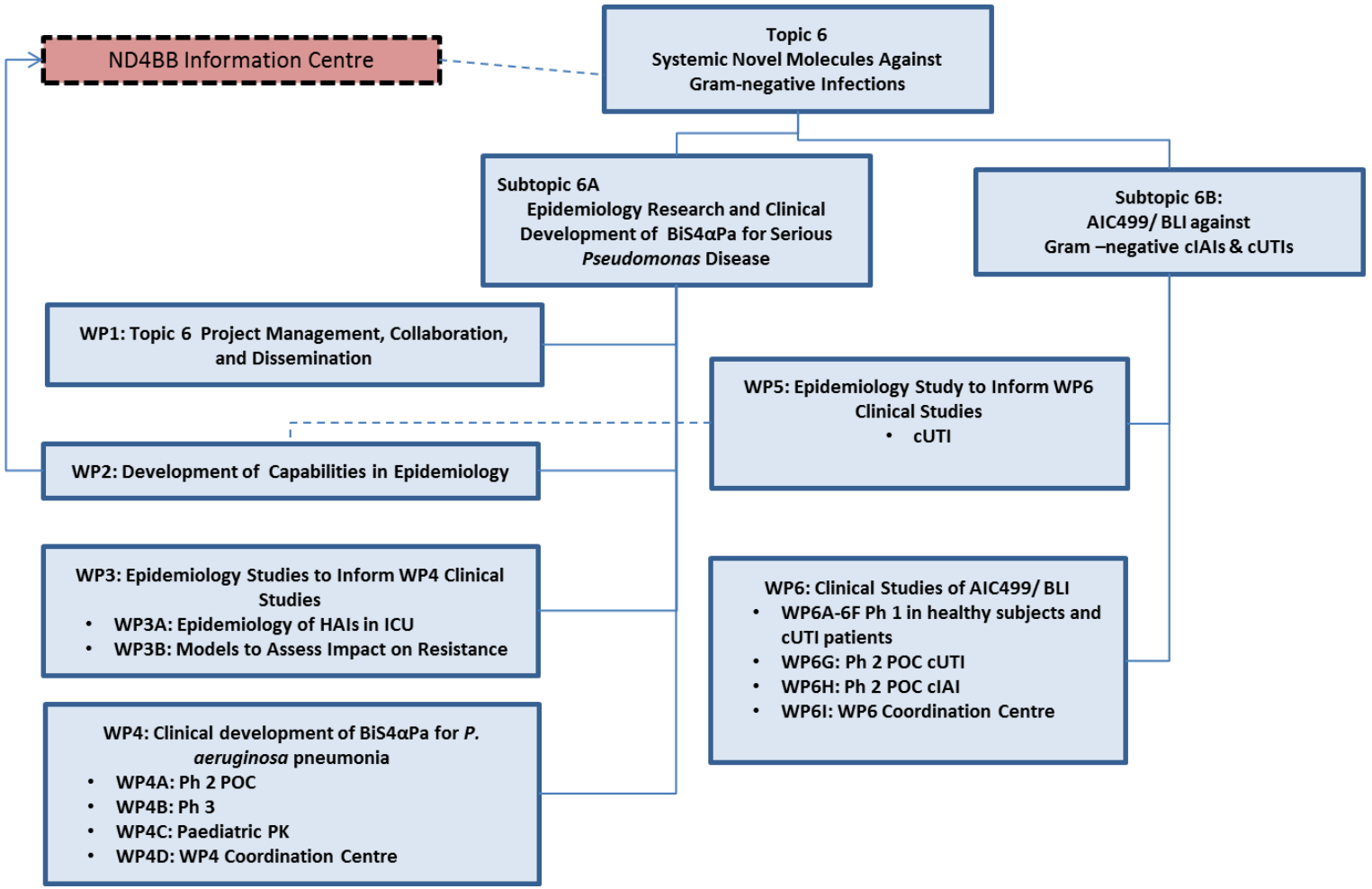


New Drugs for Bad Bugs (ND4BB) Programme



Call 6 | Call 9 | Call 8 | Call 11

ND4BB Topic 6 Framework



Topic 6: Epidemiology research and development of novel systemic antibacterial molecules against healthcare-associated infections due to Gram-negative pathogens

- **Objectives:**
  - To develop a coherent epidemiology strategy and organise pertinent expertise and available data sources in Europe and across ND4BB in support of public health and drug development priorities related to antimicrobials
  - Describe epidemiology of HAIs due to *P. aeruginosa* and other Gram-negative pathogens to help support the development of novel molecules against these infections
  - Estimate the impact of preventive or therapeutic interventions against serious *P. aeruginosa* disease, and any impact on antimicrobial resistance of *P. aeruginosa*
  - Clinical development of BiS4αPa, a novel anti-pseudomonal antibody for the prevention of *P. aeruginosa* ICU pneumonia
  - Clinical development of a novel resistance-breaking beta-lactam antibiotic, AIC499, in combination with a beta-lactamase inhibitor (BLI) for the treatment of severe bacterial infections due to Gram-negative pathogens, including complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs)

Subtopic 6A:

Clinical Development of BiS4αPa, an anti-Pseudomonas Antibody

Hasan Jafri, MedImmune

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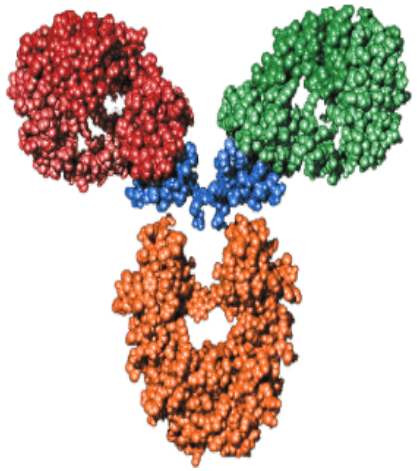
Subtopic 6A: Programme Overview

- WP1: ND4BB Topic 6 coordinating center
- Epidemiology
  - WP2: Development of programme capabilities in epidemiology
  - WP3: Epidemiology studies supporting the development of anti-pseudomonal drugs
    - WP3A: Prospective cohort study of healthcare-associated infections (HAIs) attributed to *P. aeruginosa* among intensive care unit (ICU) patients in the EU
    - WP3B: Impact of different interventions on *P. aeruginosa*-attributed disease burden among ICU patients
- WP4: Clinical Development of BiS4αPa
  - WP4A: Phase 2 Proof of Concept (POC) study to evaluate activity of BiS4αPa against *P. aeruginosa* VAP
  - WP4B: Phase 3 study to evaluate efficacy of BiS4αPa against *P. aeruginosa* VAP
  - WP4C: Paediatric safety and PK study
  - WP4D: Coordination Centre

Antibacterial Antibodies: Why?

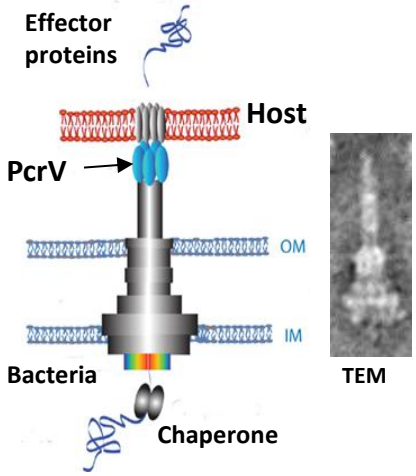
- **Specificity**
  - Would not cause cross resistance in other bacteria
  - No perturbation of the beneficial microbiome
- **Safety**
  - No host target: likely favorable safety profile
  - No drug-drug interactions
- **Long half-life**
  - Potential for single dose protection
- **Complementary mAb MOAs with antibiotics**
  - Enhance host response
  - Bacterial clearance, inhibition of colonization and cytotoxicity
  - Reduce virulence and potential for hyperinflammatory sequelae
- **Antibiotic preservation**
  - mAb MOA will not select for resistance to small-molecule antibiotics
  - Adjunctive use could reduce the potential for resistance development
  - Antibody prophylaxis could decrease prophylactic antibiotic usage



Dual Specificity: Two Key *P. aeruginosa* Targets24

PcrV

T3SS Complex



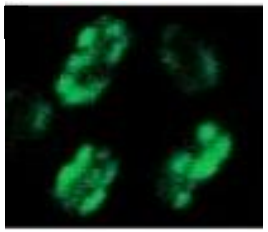
Psl: abundant surface exopolysaccharide important for adherence and biofilm formation

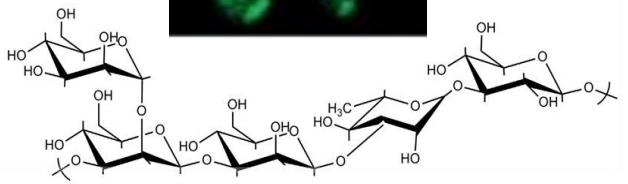
MOA: opsonophagocytic killing and anti-cell attachment

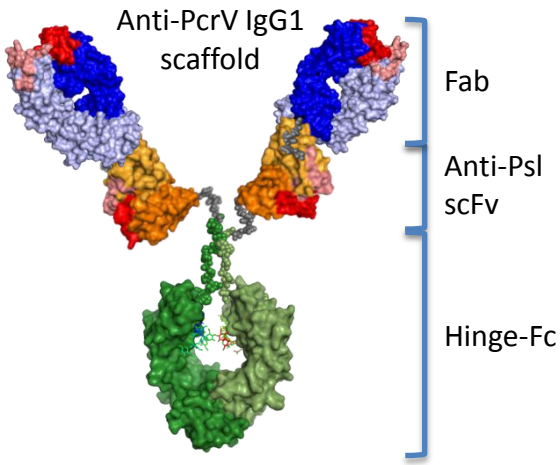
PcrV: forms the tip of T3SS responsible for injection of multiple virulence factors into host cells

MOA: prevent injection of toxins into host cells

Psl Exopolysaccharide





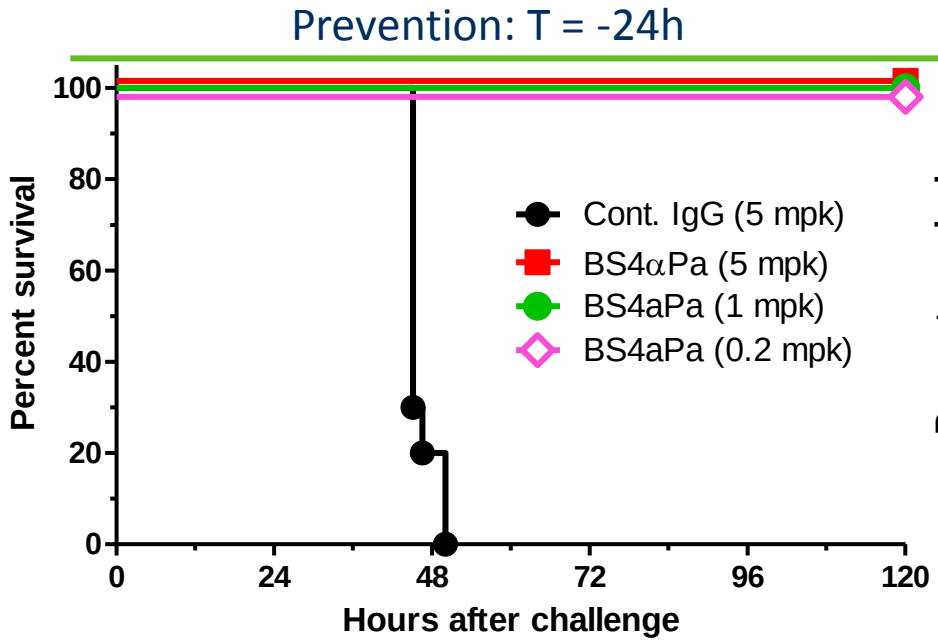


BiS4αPa

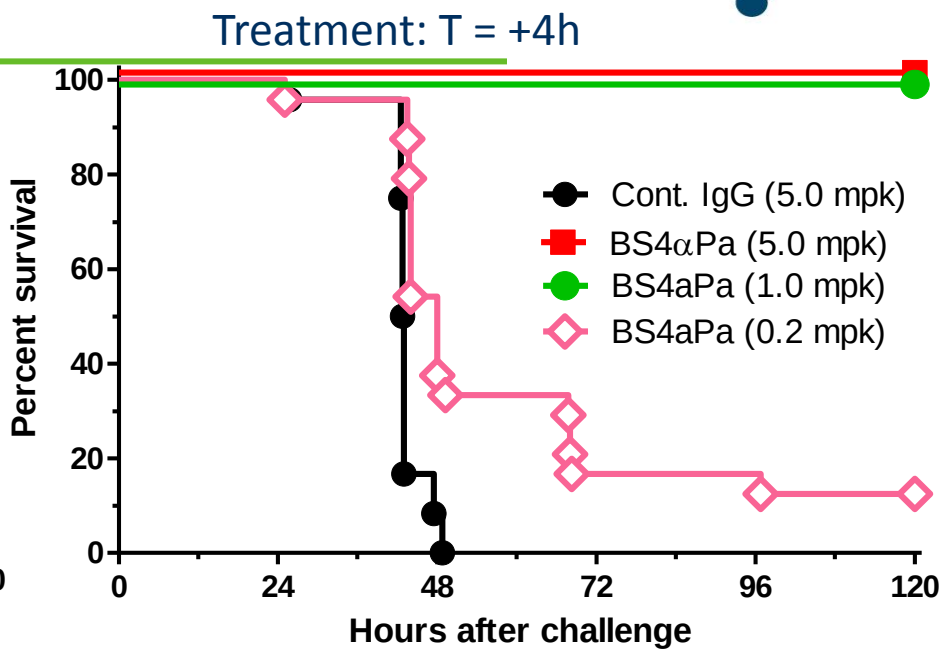
BiS4αPa

- Novel bispecific mAb with **both** anti-Psl and anti-PcrV MOAs
- Ability to engage both surface targets without competition
- Expression of both targets is reciprocally regulated
- 98% of strains express either or both targets
- Both prophylactic and therapeutic activity in-vivo

BS4αPa: Activity in murine acute pneumonia model



N=10 mice/group



N=10 mice/group

- Potent protection against *P. aeruginosa* cytotoxic strain 6077 (5X LD100)
- Both prophylactic and therapeutic activity
- Promising activity against a range of representative *P. aeruginosa* isolates
  - Cytotoxic, invasive, low Psl, high Psl

Subtopic 6A, Epidemiology: WP2

WP2: Development of programme capabilities in epidemiology

The overarching objectives are to coordinate and share data across ND4BB epidemiology studies and to engage external stakeholders to increase our collective scientific knowledge about the distribution and determinants of bacterial infections in Europe.

The WP2 team will aim to:

- Avoid duplication, by coordinating with public health authorities, academic and industry partners
- Inform current and future ND4BB efforts, by identifying and cataloguing ongoing epidemiologic research studies or surveillance activities
- Articulate a comprehensive epidemiologic strategy, by establishing a network of experts from academia, public health agencies, research/health foundations, and industry.
- Address research needs, by pursuing agreements to receive, store, and analyse study data from ND4BB and external data sources

Subtopic 6A, Epidemiology: WP3

WP3A: Prospective cohort study of healthcare-associated infections (HAIs) attributed to *P. aeruginosa* among intensive care unit (ICU) patients in the EU

- Builds upon data collection in Call 8-Subtopic 1C-WP6A, which is a prospective observational study of 2,000 ICU patients in 6-12 EU countries (2014-2016)
- Overarching goal is to identify the patient subgroups that bear a disproportionate disease burden, in order to optimize patient selection for clinical trials
- The study objectives of WP3A are to:
  - Estimate the incidence of ICU pneumonia, including ventilator-associated pneumonia (VAP), attributed to *P. aeruginosa*
  - Ascertain factors (e.g., patient demographics, co-morbidities, colonization status, biomarkers) independently associated with ICU pneumonia and attributable to *P. aeruginosa*
  - Describe antimicrobial susceptibility patterns and the prevalence of antigen expression and virulence factor profiles among clinical *P. aeruginosa* isolates from ICU patients with serious disease, including pneumonia
  - Explore the association of host biomarkers (e.g., pre-existing antibodies against *P. aeruginosa* virulence factors) with ICU infection, disease severity, and outcomes
  - Obtain cost and resource utilization data in these patients for use in cost-effectiveness analyses

Subtopic 6A, WP3: Epidemiology

WP3B: Impact of different interventions on *P. aeruginosa*-attributed disease burden among ICU patients

- Overarching goal is to develop mathematical models to estimate the serious *P. aeruginosa* disease averted by the development of successful interventions for its prevention or treatment.
- It is envisioned that model inputs will be collected from relevant epidemiologic and clinical studies within ND4BB (e.g., Topics 1, 5, 6, 7) and external sources
- The study objectives of WP3B are to:
  - Estimate the burden of disease attributed to *P. aeruginosa* and the development of antimicrobial resistance to *P. aeruginosa* among ICU patients
  - Estimate the impact of different interventions on the burden of disease attributed to *P. aeruginosa* and on the development of antimicrobial resistance to *P. aeruginosa* among ICU patients

WP3C: Epidemiology Coordination Center

The purpose of WP3C is to establish an epidemiology coordinating center to provide program management, project coordination, and strategic alignment across all epidemiology projects across Topic 6 and ND4BB.

Subtopic 6A, WP4: Clinical Development of BiS4αPa

WP4A: Phase 2 proof-of-concept study to determine safety and efficacy of BiS4αPa for the prevention of serious disease caused by *P. aeruginosa*

- **Objectives:**
  - Determine safety and tolerability of BiS4αPa in high-risk ICU population at risk for serious *P. aeruginosa* infection
  - Determine efficacy of BiS4αPa against
    - *P. aeruginosa* disease, mortality, disease severity
  - Determine PK-PD in serum and ELF, ADA in serum
  - Describe biomarkers associated with disease onset and/or outcome
- **Design:**
  - Phase 2, randomized, placebo-controlled, dose-ranging study
  - Enriched at-risk population, eg. mechanically ventilated and colonized with *P. aeruginosa*
  - Approximate sample size: 492 subjects, in EU (~ 120 sites)
  - Final study population and endpoints will be informed by the epidemiology and biomarker studies and by EMA input into acceptable endpoints.
    - » Applicants are expected to propose a population at ≥ 20% risk of developing *P. aeruginosa* pneumonia while in the ICU.

Subtopic 6A, WP4: Clinical Development of BiS4aPa

WP4B: Phase 3 study of BiS4αPa efficacy and safety

- **Objectives:**
  - Demonstrate the efficacy of BiS4αPa for the prevention of serious disease caused by *P. aeruginosa*
  - Demonstrate safety, PK and ADA associated with BiS4αPa
- **Design:**
  - Phase 3, randomized, placebo controlled
  - Approximate sample size 980 subjects, 50% in EU
  - The study design, endpoints including relevant biomarkers, and study population will be informed by epidemiology data and by data from the Phase 2 study as well as by input from regulatory authorities.

Subtopic 6A, WP4: Clinical Development of BiS4aPa

- **WP4C: Paediatric study to assess the safety and PK of BiS4αPa in high-risk subjects**
  - Objectives:
    - Demonstrate safety and PK of BiS4αPa in high-risk infants and children to provide dosing guidelines in paediatric populations
  - Design:
    - Open-label, ascending dose
    - High-risk paediatric patients from multiple age groups
    - Approximate sample size 40 subjects, in EU
- **WP4D: Coordination Centre**
  - To provide program management and project coordination, and to ensure strategic alignment within WP4, Subtopic 6A, Topic 6, and with other programmes within ND4BBs

Subtopic 6A: Stepwise/ Staggered Approach

- Call 11, ND4BB, Subtopic 6A to include information on indicative budgets of entire WP2, WP3 and WP4
- EOIs expected on entire Subtopic 6A
- WP3A to start first and inform the design of WP4A (Ph 2)
- WP4A (Ph 2) results will inform the design of WP4B (Ph 3)
- The allocated funding for WP4A-C will be released later
  - Design of WP 4A and 4B may be subject to changes on the basis of the results of the epidemiological study, and regulatory input
  - Consortium including the sponsoring EFPIA partner to determine the need for an Open Call to engage additional clinical sites/beneficiaries to run the 2 clinical studies (WP4A-B) based on the updated study details

Expected contributions of the applicants: Subtopic 6A

- Experts in active-surveillance, observational epidemiology, and clinical studies in ICU bacterial infections to participate in pan-European consortium
- Expertise in immunointervention or prophylaxis for infectious diseases in the ICU populations
- Expertise in paediatric PK studies
- Project leadership and coordination infrastructure
- Data storage, processing, and analysis capabilities
- Hospital and healthcare institutions to join a clinical trial network with capability to run Phase 1, 2 & 3 clinical trials and epidemiology surveillance studies
- Experts in diagnostics suitable for use in clinical trials, and in novel biomarker research
- Coordination & conduct of microbiology surveillance programs
- Clinical research organisation with relevant global experience

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Expected (in-kind) contributions of EFPIA members: Subtopic 6A

- Clinical trial expertise
- Expertise in designing infectious disease epidemiology surveillance programmes and research studies
- Knowledge & expertise in antimicrobials R&D
  - Provision of study drug, regulatory support, project management, pharmacovigilance, clinical expertise, etc.
  - Training/oversight of clinical sites and labs to ensure they are “audit ready.”
- Non- Europe component of the clinical trial
- Project/alliance management personnel
- Workshops/seminars/Q&As.
- Statistics, PK/PD modeling & simulation expertise
- Clinical micro procedures/protocols/serology assays required in clinical trials
- Supplement study costs (up to 25%) incurred by public partners
- Gene sequencing/gene expression of *P. aeruginosa* virulence factors

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Subtopic 6B:

Clinical development of a Gram-negative resistance-breaking beta-lactam antibiotic, AIC499, in combination with a beta-lactamase inhibitor (BLI)

Cuong Vuong & Fabian Bernal
AiCuris

AIC499 – an innovative beta-lactam antibiotic

- A novel beta-lactam (sub)class
- Excellent broad antibacterial potency
- Strongly increased beta-lactamase stability
- *P. aeruginosa* and *Enterobacteriaceae* focus (additional non-fermenter coverage)
- Antibacterial activity further improved by combination with a BLI (e.g. clavulanic acid or modern BLI)
- *in vitro* microbiology and *in vivo* animal studies indicate:
  - Broad coverage (target pathogens / resistance)
  - Excellent potency
  - Low propensity for induced resistance
- Ongoing preclinical program for intravenous (iv) administration of AIC499
- Planned First in human trial Q4/2014 – Q1/2015 (not part of IMI program)

Antibacterial Activity of AIC499

- AIC499 shows wild-type MICs for 75% of multi-drug resistant *P. aeruginosa*

  → Promising activity against *P. aeruginosa* including MDR isolates

- AIC499 with and w/o CLAV shows excellent activity against Gram-negatives incl. MDR-clinical isolates

- AIC499 + BLI: potential to treat a vast proportion of infections caused by Gram-negative wild-type and MDR pathogens

Subtopic 6B: Programme overview

- WP5: Epidemiology Workstream
  - Retrospective observational study to assess the clinical management and outcomes of hospitalized patients with complicated urinary tract infections (cUTI)

- WP6: Clinical Workstream
  - WP6A-F: Phase 1 multiple dose, Mass balance/ metabolites identification, TQT, drug-drug interactions, and renal impairment trials in otherwise healthy subjects, and cUTI patients
  - WP6G-H: Phase 2 Proof of Concept (PoC) studies to evaluate the efficacy of AIC499/BLI in cUTI and cIAI due to Gram-negative pathogens
  - WP6I: Coordination Centre

Subtopic 6B
WP5 (Epidemiological study)

- Study rationale
  - To assess clinical management and outcomes of patients with cUTI in the EU
- Key study objectives
  - To characterize the distribution of demographic factors
  - To assess antibiotic resistance patterns
  - To assess clinical outcomes, clinical management, and cost and resource utilization
  - To ascertain the frequency of treatment failures due to general risks and treatment failures related to documented antibiotic resistance
- Design
  - Multinational, multicentre, observational, retrospective cohort study of hospitalized patients with cUTI diagnosed within 2-years prior to study start
- Coordinated with WP2: Development of Capabilities in Epidemiology

Subtopic 6B
WP6A-F (Phase 1 studies)

- **WP6A:** Multiple dose trial of AIC499 in healthy volunteers (Part A) and afterwards generation of early safety and microbiological efficacy data of AIC499/CLAV from patients with cUTI without pyelonephritis (Part B)
- **WP6B:** Drug-drug interaction trial between AIC499 and BLI to investigate their mutual influence on pharmacokinetics and safety
- **WP6C**: Pharmacokinetics and mass balance study of AIC499, and identification of its metabolites in humans
- **WP6D**: TQT prolongation study to obtain guidance for cardiac safety monitoring in studies with larger populations
- **WP6E**: Drug-drug interactions between AIC499/BLI and usual concomitant medication in the intended indications
- **WP6F**: Effect of different degrees of renal impairment in patients on the pharmacokinetics of AIC499

Subtopic 6B
WP6G-I (Phase 2 studies)

- **WP6G**: PoC trial in hospitalised patients with cUTI due to Gram-negative pathogens
- **WP6H**: PoC trial in hospitalised patients with cIAI due to Gram-negative pathogens
  - To investigate the safety, tolerability, efficacy and pharmacokinetics/ pharmacodynamics of AIC499/BLI in patients with cUTI or cIAI
  - To assess the efficacy of AIC499/BLI in cases caused by multi-drug resistant Gram-negative pathogens
- **WP6I**: Clinical workstream (WP6A-H) coordination cente
  - To provide program management and project coordination, and to ensure strategic alignment within Subtopic 6B, Topic 6, and with other programs within ND4BBs

Subtopic 6B: Stepwise/ Staggered Approach

- Call 11, ND4BB, Subtopic 6B to include information on indicated budget of entire WP5 and WP6
- EOIs expected on entire Subtopic 6B
- WP5 to start after formation of consortium
- WP6A-F results will impact the design of WP6G-H (Phase 2 PoC)
- The allocated funding for WP6 may be subject to changes on the basis of the results of the AiCuris SD study and regulatory input
- Consortium including the sponsoring EFPIA partner to determine the need for an Open call to engage additional clinical sites/ beneficiaries to run the clinical studies (WP6A-H) based on the updated study details

Expected contributions of the applicants: Subtopic 6B

- Expertise in infectious disease epidemiologic studies design and execution
- Expertise for conducting early Phase 1 studies
  - Available facilities for standard Phase 1 studies, including PK samples processing, standardised measurements of ECG, vital signs, safety lab and regular Adverse Events questioning
  - Expertise in conducting accelerated mass spectrometry (AMS) studies
- Expertise in innovative Phase 2 multicentric clinical trial design and management
  - Expertise in standard of care for cUTI and cIAI
  - Experience in clinical study with antibacterial treatments
  - Processing of clinical microbiological samples and resistance determinations
- Large healthy volunteer and patient databases

Expected (in-kind) contributions of EFPIA members: Subtopic 6B

- Knowledge and expertise in antimicrobials R&D
- Phase 1 and phase 2 clinical trials expertise
  - Training/oversight of clinical sites and labs to ensure they are "audit ready."
  - Regulatory support, project management, pharmacovigilance
- Project/Alliance management personnel
- Workshops/seminars/Q&As.
- Provision of study drug
- Supplement study costs (up to 25%) incurred by public partners

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Questions?

- Contact the **IMI Executive Office**

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Website: www.imi.europa.eu