

**Control Number:** 2023-A-63-ASM-ESC  
**Session Title:** **Rapid Fire Presentations I**  
**Publishing Title:** **Exploring the Views of Infection Consultants in England on a Novel Delinked Funding Model for Antimicrobials: the SMASH study**  
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**Abstract Body:** **Background**A novel “subscription-type” funding model was launched in England in July 2022 for ceftazidime-avibactam and cefiderocol. We aimed to collect the views of English infectious diseases and microbiology consultants (“attending physicians”) on important aspects of the delinked funding model.**Methods**This was a national online survey of all infectious diseases and microbiology consultants working in acute hospitals of the National Health Service (NHS) in November and December 2022.**Results** The final response rate was 31.2% (235/753). Most consultants thought the model is a welcome development (69.8%, 164/235), will improve treatment of drug-resistant infections (68.5%, 161/235) and will stimulate research and development of new antimicrobials (57.9%, 136/235). Consultants disagreed that the model will lead to reduced carbapenem use and reported increased cefiderocol use post implementation ( $p < 0.001$ ). The presence of an antimicrobial pharmacy team, requirement for preauthorization by infection specialists, antimicrobial stewardship ward rounds and education of infection specialists were considered the most effective antimicrobial stewardship interventions for preserving the efficacy of the “subscription-type” antimicrobials. Pre-authorization by an infection specialist to access the model antimicrobials was universally agreed (98.7%, 232/235). Under the new model, 42.1% (99/235) of consultants would use the new antibiotics empirically, if risk factors for antimicrobial resistance were present. Significantly higher insurance and diversity values were given to model antimicrobials compared to other established treatments for carbapenem-resistant infections, while meropenem recorded the highest enablement value and fosfomycin the highest spectrum value. Use of both subscription drugs for infection sites outside of their licenced site-specific indications was reported, especially for cystic fibrosis-bronchiectasis. Ceftazidime-avibactam was prioritized for OXA-48 and KPC infections, while cefiderocol for metallo-beta-lactamase infections, infections from *Stenotrophomonas maltophilia*, *Acinetobacter spp*, *Burkholderia cepacia*.**Conclusions.**A “subscription-type” model was seen favourably by infectious diseases and microbiology consultants in England. “Subscription-type” funding models might be important solutions for access to novel antimicrobials and for revitalising the antimicrobial research and development pipeline.

**Control Number:** 2023-A-93-ASM-ESC  
**Session Title:** **Rapid Fire Presentations I**  
**Publishing Title:** **Novel Inhibitors of the Two-Component System VanRS Re-sensitize *Enterococcus Faecalis* to Vancomycin**

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**Abstract Body:** **Background:** Two-component systems (TCS) are the main bacterial signalling systems and are involved in adaptation, virulence, antimicrobial resistance, etc. TCS are formed by a sensor Histidine Kinase (HK) that after stimuli detection undergoes autophosphorylation via an ATP bound to the catalytic domain (CA). Then there is a phosphotransfer to the Response Regulator (RR) that changes gene expression accordingly. TCS have been proposed as good antibiotic targets due to the presence of multiple TCS in all bacteria, conservation of CA domains and absence in mammalian cells. Here, we used a fragment-based drug design approach to develop inhibitors that compete with ATP for the ATP-binding pocket on the CA domain of TCS. We found an inhibitor that re-sensitizes *E. faecalis* to vancomycin treatment by inhibition of VanRS TCS.

**Methods:** We screened a series of fragments *in silico* for binding to the ATP-pocket of different HKs. The most promising were synthesized and binding was confirmed via X-crystallography. The most promising fragment CT04 was rationally grown into a compound library what was synthesized, screened for *in vitro* binding to HKs using MST and *in vivo* inhibition of key TCS such as VanRS in enterococci.

**Results:** All compounds bound *in vitro* to the HKs CheA from *Thermotoga maritima* and PhoR from *Staphylococcus aureus* with K<sub>d</sub> of best compounds in the low μM range. We found that library compounds containing sulfone groups significantly reduced vancomycin resistance in *E. faecalis* and *E. faecium*. Surprisingly, compound 752 completely re-sensitized *E. faecalis* vanA and vanB to vancomycin. Expression analysis showed a significant downregulation of the *vanA* induction due to vancomycin treatment. Compound 752 failed to re-sensitize *E. faecium* to vancomycin, but showed a similar reduction in *vanA* induction.

**Conclusions:** Novel TCS inhibitor 752 re-sensitizes *E. faecalis* to vancomycin treatment by partially inhibiting VanRS TCS. Compound 752 also partially inhibits VanRS in *E. faecium* but not enough to re-sensitize it to vancomycin. Optimization for stronger inhibition of VanRS could serve to re-sensitize enterococci to vancomycin, with great implications in nosocomial infections.

**Control Number:** 2023-A-96-ASM-ESC

**Session Title:** **Rapid Fire Presentations I**

**Publishing Title:** **Development of a Rabbit Model of Nosocomial Pneumonia to Combat Emergence of Resistance**

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**Abstract Body:** **Background** Relatively few active antibiotics are available for nosocomial pneumonia. Antimicrobial resistance contributes to unacceptably high rates of morbidity and mortality. Current model systems used for developing new antimicrobials for pneumonia have several limitations. Here, we describe a new rabbit pneumonia model allowing antibacterial activity and the emergence of resistance to occur. We used this

model to characterise the pharmacokinetics and pharmacodynamics of meropenem alone and in combination with amikacin.

**Methods** A 96h experimental model of nosocomial pneumonia was developed in NZW rabbits, allowing a clinically relevant background immunosuppression and pathogenesis to be recapitulated. Cytosar-U was administered daily as an immunosuppressant. *P.aeruginosa* was inoculated intratracheally, resulting in a progressive bronchopneumonia, which was universally lethal beyond 96h without treatment. Meropenem and/or amikacin were administered q8h parenterally starting 24h post infection. Blood and lung samples were taken for PK, PD analysis respectively. A satellite study was performed to collect and fix lung samples for histopathological analysis. A PK-PD mathematical model was fitted to the PK/PD data using Pmetrics.

**Results** Histopathological analysis showed progressive bronchopneumonia with severity of infection increasing in a time-dependent fashion. Meropenem 30mg/kg q8h was effective at limiting the pulmonary inflammation, tissue damage, and bacterial growth at 96h post infection. Meropenem monotherapy demonstrated a linear exposure-effect response for bacterial killing and an 'inverted U' relationship for emergence of resistance. The addition of 3.33mg/kg or 5mg/kg amikacin q8h to meropenem 5mg/kg q8h did not increase bacterial killing, but did suppress emergence of resistance. A three-compartment structural PKPD model described the data well, with the exposures of 30mg/kg q8h comparable to meropenem 500 mg q8h IV in humans.

**Conclusions** The PD of meropenem and amikacin have been quantified in this model of nosocomial pneumonia with the combination of agents successful in limiting the emergence of resistance. This model can be used to assess the activity of new agents and combination therapies for nosocomial pneumonia.

**Control Number:**2023-A-97-ASM-ESC

**Session Title:** **Rapid Fire Presentations I**

Targeting *Aspergillus fumigatus* hypoxia response pathways for novel antifungal drug development

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*Aspergillus fumigatus* is a ubiquitous filamentous fungus that contributes to significant human morbidity and mortality. There are currently only three contemporary antifungal therapies to treat aspergillosis in all its manifestations. Their efficacy in established infections is sub-optimal. Moreover, rapidly increasing resistance to first line therapy triazole therapies highlights a significant need to develop novel antifungals with innovative mechanisms of action. Research from our lab has observed that the fungal hypoxia response, mediated by the transcriptional regulator SrbA, is a promising antifungal target necessary for virulence and azole resistance in *Aspergillus fumigatus* and other human pathogenic fungi. To identify inhibitors of the SrbA mediated hypoxia response pathway, we developed a novel

cell-based antifungal assay strain and used it to screen over 200,000 small molecule compounds for antifungal activity in the presence of fluconazole or hypoxic conditions. Using this high-throughput screen we identified MBX-7591: a novel small molecule with minimal human toxicity that has exhibited proof-of-principle in vivo efficacy in a mouse model of invasive pulmonary aspergillosis. MBX-7591 has increased activity in hypoxic conditions and in the presence of azoles, conditions relevant to *A. fumigatus* infections. Preliminary mechanism of action data suggest that MBX-7591 is acting through the SrbA-dependent hypoxia response pathway to disrupt cell membrane homeostasis by altering lipid composition. Taken together, these data suggest MBX-7591 is a promising antifungal agent with a novel mechanism of antifungal action.