TABLE 1. Synergistic effect of sulbactam, colistin, and fosfomycin sodium with biapenem against MDR A. baumannii (n = 40) by using the checkerboard assay

	Number of Isolates (%)		
Effect	Sulbactam + Biapenem	Colistin + Biapenem	Fosfomycin sodium + Biapenem
Synergy (FICI≤0.5)	30 (75)	40 (100)	33 (82.5)
Partial synergy (FICI>0.5-<1)	9 (20)	0	7 (17.5)
Additive (FICI=1)	1 (5)	0	0
Indifference (FICI>1-≤4)	0	0	0
Antagonism (FICI>4)	0	0	0

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1535. Nitric Oxide-Releasing Chitosan for the Treatment of Multi-Drug Resistant Superbugs

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Background. Multi-drug resistant superbugs are a serious health threat due to limited treatment options and high mortality rates. Certain superbug strains are now resistant to as many as 36 representative FDA-approved antibiotics, including Colistin and Carbapenem antibiotics, widely considered as the last line of defense against untreatable infections. Nitric oxide (NO) is a diatomic free radical employed by the immune system to eradicate bacteria via oxidative and nitrosative stress. To facilitate storage and controlled release of NO, we have developed NO donor-modified biopolymers based on chitosan, a linear polysaccharide composed of randomly distributed β--linked D-glucosamine and N-acetyl-D-glucosamine. Herein, we report the broad spectrum antibacterial action of low molecular weight (5 kDa) NO-releasing chitosan against Gram-positive and Gram-negative multi-drug-resistant bacterial species, including *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.

Methods. MIC assays were performed using CLSI guidelines in a 96-well plate format. All assays were carried out in triplicate using a two-fold dilution range. The bacterial suspension was then diluted in assay medium to a target concentration of approximately 5×10^5 CFU/mL, after which it was added to all test and growth control wells, and allowed to incubate. Test wells were scored for the lowest NO concentration released from the chitosan to inhibit visual growth of the pathogen. After MIC determination, wells demonstrating inhibition were plated, incubated and resulting colonies counted to determine survival concentration. The lowest concentration of NO to inhibit ≥99.9 % of a given test organism was reported as the MBC. Of note, chitosan alone showed no antibacterial action.

Results. MIC and MBC assays for NO-releasing chitosan against six multi-drug resistant strains are provided below.

Organism	Resistance	Source	MIC (μmol/ml)	MBC (μmol/ml)	Notes
Klebsiella pneumoniae	NDM-1	ATCC BAA-2146	0.43	1.7	
Methicillin-Resistant Staphylococcus Aureus (MRSA)		ATCC 33591	0.27	4.25	
Klebsiella pneumoniae	KPC	AR-BANK#0097	0.85	1.7	
Klebsiella pneumoniae	TEM-1, SHV-11, CTX-M15	AR-BANK#0109	0.85	1.7	Colistin resistant strain
Pseudomonas Aeruginosa	KPC	AR-BANK#0231	0.43	0.85	Tobramycin resistant strain
Pseudomonas Aeruginosa	NDM-1	AR-BANK#0246	0.43	0.85	Tobramycin resistant strain

Conclusion. The properties of the NO-releasing chitosan, including water solubility, make it an excellent drug candidate for treating respiratory infections. Such development is currently underway.

Disclosures. **All authors:** No reported disclosures.

1536. Discovery of Antifungal Compounds from Kampo Medicine Against Dermatophytes

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Background. Kampo medicine mainly contain crude extracts of natural products such as plants, animals, and minerals that are prepared according to classical Kampo methodologies. Since plants synthesize numerous antimicrobial components such as plant defensins, Kampo medicine likely contain potent antimicrobial constituents. We have tested antifungal activity of 61 commercially available Kampo medicines by using micro-broth dilution assay with *Trichophyton rubrum* (*T. rubrum*), and found that 7 of them had antifungal activity. Among these 7 Kampo medicines 6 contained Ou-gon which derived from the roots of *Scutellaria baicalensis Georgi*, and a crude extract of Ou-gon exhibited significant antifungal activity. This study aims to identify antifungal components contained in Ou-gon, and determine their antifungal mechanism.

Methods. *T. rubrum*, *T. mentagrophytes*, *Aspergillus fumigatus* (*A. fumigatus*) and *Candida albicans* (*C. albicans*) were used for antifungal activity assay. The antifungal activity assay was performed by measuring 595 nm absorbance in micro-broth dilution assay. Active components were analyzed by high performance liquid chromatography (HPLC), and identified by liquid chromatography electrospray ionisation mass spectrometry (LC-ESI-MS/MS). TUNEL assay, SYTOX-Green Uptake analyses, intracellular reactive oxygen species accumulation assay, mitochondrial membrane potential assay, scanning electron microscopy, and transmission electron microscopy were used to clarify the antifungal mechanism of active components.

Results. Upon HPLC analysis, two low molecular weight-compounds were isolated having potent antifungal activity. The two compounds were identified as Baicalein and Wogonin by LC-ESI-MS/MS. Baicalein showed antifungal activity for *T. rubrum*, *T. mentagrophytes*, *A. fumigatus* and *C. albicans*. Wogonin showed antifungal activity for all except *C. albicans*. Detection of antifungal mechanism of Baicalein and Wogonin suggested that their mode of action is apoptosis-like programmed cell death.

Conclusion. Baicalein and Wogonin are major compounds to have antifungal activity in Kampo medicine. This study may contribute to the development of new and safe antifungal drugs, especially for the clinical treatment of pathogenic fungal infections.

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1537. Feasibility of Neurapheresis™ as a Therapy for Multidrug Resistant Gram-negative Bacterial Meningitis

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Background. The World Health Organization has identified *Pseudomonas, Acinetobacter* and *Klebsiella (PAK)* as three multidrug resistant (MDR) gram-negative pathogens that pose a threat to human health. The greatest threat lies in hospitals, nursing homes, and patients with devices such as intravenous catheters and ventilators. Gram-negative bacterial meningitis (GBM) manifests when these bacteria invade the central nervous system. Due to the threat of increasing antibiotic resistance and the high mortality associated with MDR GBM, we have tested a closed-loop, extracorporeal cerebrospinal fluid (CSF) filtration system (*Neurapheresis™*) for its applicability in this context. Here we demonstrate feasibility of Neurapheresis for MDR GBM and characterize system parameters for bacterial clearance.

Methods. *PAK* cultures were grown and diluted to 1×10^7 cells/mL in artificial CSF or Luria-Miller broth. Both single pass and closed loop filtration were performed with various tangential flow filtration (TFF) and dead-end filter paradigms. Samples were taken either immediately post-filter or after every full CSF volume cycle (150 mL) during a long-term closed loop experiment. Bacterial load, endotoxin and cytokines were quantified.

Results. In single pass tests, 5kDa and 100kDa TFF filters and 0.2μm and 0.45μm dead-end filters excluded all *PAK* organisms completely. The 100kDa and 5kDa TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters demonstrated a 1–2 Log CFU (90–99%) reduction of all *PAK* organisms over 4 filtration cycles.

Conclusion. Neurapheresis shows potential to be an efficient multi-modal tool for controlling and treating MDR GBM in this *in vitro* model. Extending closed loop filtration over time demonstrates capability for rapid sterilization of the CSF. Future iterations may include adjunctive intrathecal drug delivery to further accelerate elimination of bacteria. Reduction of both endotoxin and cytokines by Neurapheresis may have significant implications for controlling the damaging neuro-inflammatory response during MDR GBM.

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