Plazomicin is an aminoglycoside designed to overcome the vast bulk of aminoglycoside modifying enzymes, the most common aminoglycoside resistance mechanism in Enterobacteriaceae. Plazomicin is FDA approved for cUTI/pyelonephritis. An additional study in patients with CRE serious bacterial infections has been conducted. Dose-range studies in a neutropenic murine thigh infection model (TIM) and a neutropenic murine pneumonia model (NPM) of CRE infection and dose fractionation studies in the TIM were performed to identify the PD index and exposure intensities that optimize the killing of CRE in each infection site. Pharmacokinetic studies were carried out, including ELF penetration studies, to link mg/kg/day doses to PD exposure indices. Understanding the PD index and exposure targets allows identifying optimal doses and schedules in man to attain the best clinical results.

• How does site of infection influence exposure target?

Materials & Methods

Organisms for Study
Eight K. pneumoniae, E. coli and Enterobacter strains were evaluated in dose-range studies for plazomicin in the neutropenic TIM. Seven were used for the NPM studies. The strains were selected and supplied by Achaogen, Inc. Some of the isolates were resistant to one or more carbapenem antibiotics and/or to the legacy aminoglycoside gentamicin, tetracycline or amikacin. In vitro Susceptibility Testing
The in vitro susceptibilities were performed using the broth microdilution method described by CLSI.

Neutropenic Murine Thigh Infection Model
Methods for TIM are shown in Abstract 101
Neutropenic Murine Pneumonia Model
All animal experimentation was approved by the University of Florida Institutional Animal Care and Use Committee. Female, 16–18 g BALB/c mice (Charles River [NCI colony], Frederick, MD) were rendered transient neutropenic with 150 mg/kg of cyclophosphamide given intraperitoneally (i.p.) 4 days prior to infection plus 100 mg/kg given i.p. 1 day before infection. The neutropenic mice were anesthetized with ketamine (i.m.) 0.3 mg/kg, Xylazine (i.m.) 0.1 mg/kg and allowed to recover from the anesthesia. Two hours after pathogen challenge, plazomicin and vehicle control were administered by the subcutaneous route at the indicated dosing schedule assigned to each group. At sacrifice, lungs were collected for colony count determination for the efficacy studies. For the PK studies plasma and bronchoalveolar lavage were collected at designated time points and plazomicin and urea concentrations were measured by LC-MS/MS.

Mathematical Analysis
Inhibitory sigmoid-Emax analysis: A 4 parameter model (Emax, EC50, E0, H) was employed to link exposure to response. Fit of the model to the data was accomplished with the Estimation module of the ADAPT V package of programs. A maximum likelihood estimator was employed. Stasis was defined as the AUC/MIC ratio exposure which was required to keep the bacterial burden at the size measured when therapy was initiated. Other Log Kill targets were also calculated. Population PK analysis was performed for all plasma and ELF determinations with the BigNAPG program. ELF penetration was calculated as the ratio of AUCELF/AUCPlasma.