Conclusion: Mupirocin is a potentially effective antibiotic against *Helicobacter pylori* including clarithromycin/metronidazole – resistant strains.

A7.3

Inhibition of SARS Coronavirus 3C-Like Protease by *Isatis indigotica* Root and Plant-derived Phenolic Compounds

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Objectives: To test *Isatis indigotica* root extract, five major compounds of Isatis indigotica root, and seven plant-derived phenolic compounds for anti-SARS CoV 3CLpro effects using cell-free and cell-based cleavage assays

Significance: The 3C-like protease (3CLpro) of SARS-coronavirus mediates the proteolytic processing of replicase polypeptides 1a and 1ab into functional proteins, becoming an important target for the drug development.

Study Design: Analytical

Methodology: Cell-free cleavage assay was carried out using transcleavage of substrate fusion protein by SARS-CoV 3CLpro, whereas cell-based cleavage assay was according to the cis-cleavage of the 3CLpro-substrate-luciferase fusion protein in Vero cells.

Results: Cleavage assays with the 3CLpro demonstrated that IC50 values were in micromolar ranges for *Isatis indigotica* root extract, indigo, sinigrin, aloe emodin and hesperetin. Sinigrin (IC50 of 217 microM) was more efficient on blocking the cleavage processing of the 3Clpro than indigo (IC50 of 752 microM) and beta-sitosterol (IC50 of 1210 microM) in the cell-based assay. Only two phenolic compounds aloe emodin and hesperetin dose-dependently inhibited cleavage activity of the 3CLpro, in which the IC50 value was 366 microM for aloe emodin and 8.3 microM for hesperetin in the cell-based assay. In addition, MTT cell proliferation assay indicated that these compounds had no-effect on cell viability.

Conclusion: Hesperetin with IC50 of 8.3 μM on the 3CLpro could be a potent inhibitor on SARS CoV. This study will be useful for development of anti-SARS drugs.

A7.4

In Vitro Antibacterial Activity of DX-619, A Novel Des-Fluoro(6)-Quinolone, Against Multidrug-resistant Gram-positive Bacteria

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Objectives: To determine the antibacterial and bactericidal activity, propensity of acquired resistance, and mode of action of DX-619 against Gram-positive bacteria, including older quinolone-resistant pathogens

Significance: Emergence of multidrug resistant Gram-positive bacteria has generated worldwide concern in the medical community. DX-619 is a novel des-F(6)-quinolone with expanded activity against Gram-positive pathogens.

Study Design: Analytical study on clinical isolates

Setting: Laboratory

Population: Gram-positive bacteria from clinical isolates

Methodology: Bacterial strains isolated clinically in Japan in 1994, 2000 and 2002 were used. Determination of MICs and time-kill study were performed according to NCCLS methods. Single and multi-step resistance studies and mutant prevention concentrations were determined for propensity of acquired resistance. Inhibitory activities on DNA gyrase and topoisomerase IV were assessed by supercoiling assay and decatenation assay, respectively.

Results: DX-619 showed the most potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci among compounds tested. Against quinolone-resistant MRSA, DX-619 had the lowest MIC50/90s (0.06/0.5 mg/ml) followed by linezolid (1/1), vancomycin (1/2), moxifloxacin (2/32), levofloxacin (8/>128), and ciprofloxacin (32/>64). Time-kill study demonstrated that DX-619 showed dose dependent and rapid killing activity against MRSA, whereas vancomycin and linezolid were bacteriostatic. Acquisitions of resistance of MRSA to DX-619 were lower than those to ciprofloxacin. The 50% inhibitory concentrations (IC50) of DX-619 against altered target enzymes of *S. aureus* were significantly lower than those of available quinolones. The IC50 values of DX-619 for altered enzymes were comparable to IC50s of the available quinolones for wild type enzymes.

Conclusion: On the basis of the high antibacterial activity and the low propensity to emerge resistance, DX-619 promised to be a valuable therapeutic option for life- threatening infections caused by multidrug resistant Gram-positive pathogens. The high antibacterial activities of DX-619 against quinolone-resistant MRSA may be attributable to its high inhibitory effect on target enzymes with quinolone-resistant alterations.

A7.5

In Vitro Antibacterial Activity Against Gram-positive and Gram-negative Pathogens in Asia - Tigecycline Evaluation Surveillance Trial (T.E.S.T.)

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Objective: To evaluate the antibacterial activity of tigecycline against Gram-positive and Gram-negative pathogens in Asia

Significance: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the *in vitro* activity of tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against Gram-negative rods in addition to linezolid, penicillin and vancomycin for the Gram-positive species. Isolates were collected from hospitals located in Asia throughout 2004.

Study Design: *In vitro* antibiotic susceptibility testing of clinical isolates

Population: Clinical isolates

Methodology: A total of 424 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to NCCLS guidelines.

Results: Tigecycline's activity was similar to imipenem against enterobacteriaceae with MIC50/MIC90 of 0.25/1 mcg/ml. Resistance to third generation cephalosporin was found in 63.2% of *E. coli* and 77.8% of *K. pneumoniae* consistent with ESBL phenotype. Tigecycline inhibited ESBL and AmpC producers with MICs equal or lesser than 1 mcg/ml. Although similar to other classes of broad spectrum antimicrobial agents against glucose non-fermenters, tigecycline was especially active against *Acinetobacter spp*. presenting the lowest MIC90 of 1 mcg/ml. Tigecycline successfully inhibited *S. aureus* with MIC90 of 0.25 mcg/ml regardless of sensitivity or resistance to methicillin. The same phenomenon was noticed against enterococci where tigecycline's MIC90 of 0.12 mcg/ml was consistent regardless of vancomycin susceptibility.

Conclusion: Tigecycline's *in vitro* activity was comparable to or greater than most commonly prescribed antimicrobials. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against both aerobic Gram-positive and aerobic Gram-negative bacteria, including multi-drug resistant strains regardless of degree or type of resistance.