Wide-Spectrum Biomimetic Antimicrobial Systems

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Emerging bacterial resistance to antimicrobial drugs represents a significant threat to human health. Unfortunately, there is a limited pipeline of drugs available to counter such threats. For example, new agents capable of addressing infections caused by gram-negative bacteria are not expected to be available for another *10-15 years*. This lack of anti-infectives is particularly worrisome for biological threat agents, where multidrug resistance may either be intrinsic or engineered. Recently, nontoxic antimicrobial polymers mimicking the structures of naturally occurring antimicrobial peptides have been designed and are under development commercially as novel therapeutics. Although these compounds are already potent, we sought to evaluate the co-application of certain sesquiterpenoid compounds (nerolidol, farnesol and bisabolol) for enhancing the antimicrobial activities of these polymers. Three low molecular weight methacrylate polymers (PolyMedix, Inc., Radnor, PA) were examined for their antimicrobial activities against *E. coli*, *S. aureus* and *C. albicans*, both alone and when co-administered with sesquiterpenoid enhancers. Methods of test included disk diffusion, CLSI broth microdilution and timecourse plating assays. Our results indicate that these sesquiterpenoids, at sub-inhibitory (micromolar) concentrations, were potent enhancers of biomimetic polymer activities for all organism/polymer combinations tested. For example, in the presence of 100µM nerolidol, the MIC of PMX 50004 for *S. aureus* was reduced from 62.5µg/ml to 3.91µg/ml as tested by broth microdilution, with similar results obtained for other organisms tested. Collectively, our results indicate the promise of this biomimetic systems approach for development of new, effective and fast-acting antimicrobial treatments. Results from preliminary screens using the NIAID category B pathogens *S. typhimurium*, *L. monocytogenes*, *Y. enterocolitica* and *E. coli* O157:H7 suggest the utility of this wide spectrum approach for addressing these and other threat agents.

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