Physical Chemistry Seminar

Tuesday, October 21, 2014 | **11:00 am** | **Room 1315 Chemistry Building**

Combating antibiotic resistance with synthetic molecular evolution: Engineering a new generation of peptide antibiotics

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Host: Professor Jim Weisshaar

The antimicrobial peptides (AMPs) have long been a promising, but unfulfilled, candidate drug class for the treatment of drug-resistant microbial infections. While many AMPs with excellent, broad-spectrum activity *in vitro* have been described, few have been shown to have clinically useful activity *in vivo*. We hypothesize that the effectiveness of AMPs *in vitro* does not translate well to clinical utility because known AMPs have one or more of the following limitations: (i) low solubility, (ii) residual toxicity, (iii) loss of activity in the presence of concentrated host cells and plasma, (iv) rapid degradation *in vivo*, and (v) high manufacturing cost due to chemical complexity (e.g. crosslinking and cyclization). We show that a major impediment to clinical utility is that all microbicidal peptides lose activity in the presence of concentrated erythrocytes. To explain this observation, we developed a label-free method to make direct measurements of peptide binding to eukaryotic and bacterial cells. These measurement show that microbe sterilization occurs only when there are tens of millions of an antimicrobial peptide bound to each microbial cell: or at least one peptide per bacterial lipid. Microbe killing is dependent on membrane saturation, which explains why resistance does not readily arise. Second, while the binding of cationic AMPs is indeed selective for the anionic membranes of microbes (on a per cell basis), the binding of AMPs to host cells can nonetheless explains the activity loss *in vivo* due to the very high concentration of host cells, *in vivo*. *The key to engineering clinical utility into AMPs is not the improvement of inherent microbicidal activity, but the reduction in host cell binding.* We are currently circumventing this roadblock (and others) using synthetic molecular evolution: iterative library design and high-throughput screening.

Refreshments will be available prior to the seminar at 10:45 a.m. outside room 1315

Graduate Students may meet with the speaker at 1:00 p.m. in Room 8305F