Development and Validation of Nisin Phage Display

Kenton Hetrick and Wilfred van der Donk

Lanthipeptides, members of the ribosomally synthesized and post-translationally modified peptide (RiPP) class of natural products, have long been recognized for their potential to serve as antimicrobial compounds. For example, the lanthipeptide nisin has been used as a food preservative for over 50 years with little resistance observed, although its rapid degradation at physiological pH renders it unsuitable as a systemic antibiotic. Recently, lanthipeptides have been tested for a wider variety of applications, including as clinical imaging agents, as a cystic fibrosis treatment, and as a *Clostridium difficile* infection treatment. Against this backdrop of tremendous clinical potential, the development of a system enabling the optimization of binding or pharmacokinetic properties of lanthipeptides through directed evolution could allow the rapid maturation of improved clinical candidates for these and a myriad of other applications. Here we report the development and proof-of-concept demonstration of a bacteriophage-based selection platform for the lanthipeptide nisin. This platform should be generally applicable to lanthipeptides and even other RiPPs. It allows future selections to optimize lanthipeptide characteristics.