Selection of cyclic lanthipeptide for disruption of protein-protein interactions

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Many important biological and pathological processes are mediated by protein–protein interactions (PPI). Using peptides or small molecules to interfere with these interactions could open the door to control over cellular events. Cyclic peptides hold much promise for inhibiting PPI due to their structural mimic of the native ligands, reduced conformational flexibility, and stability against cellular catabolism.

Lanthipeptides are a group of ribosomally produced cyclic peptides containing thioether linkages that could serve as potential candidates for PPI inhibitors. Here we described the construction of novel cyclic lanthipeptide libraries in *E. coli* with a substrate-tolerate synthetase ProcM discovered from the cyanobacteria *Prochloroloccus* MIT9313, and the *in vivo* selection for inhibitors that disrupt Tsg101-Gag interaction during HIV budding process as a proof of concept.