

## **Chemical-proteomic strategies to fight multiresistant bacteria**

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Multiresistant bacterial pathogens such as Methicillin-resistant *Staphylococcus aureus* (MRSA) are responsible for a variety of severe infections that pose a significant threat to global health. To approach this challenge new chemical entities with an unprecedented mode of action are desperately needed. This presentation will cover our latest efforts to identify new anti-bacterial targets and corresponding chemical inhibitors. A proteome mining approach will be presented to identify cofactor-dependent enzymes as novel antibiotic targets. Small molecule cofactor mimics infiltrate the bacterial metabolic machinery leading to their incorporation in PLP-dependent enzymes. Their analysis via mass-spectrometry revealed the function of uncharacterized proteins in important bacterial pathways as well as the mechanism of action of known antibiotics.

In a separate approach we identified new synthetic or natural product derived compound classes that effectively kill pathogenic bacteria. Chemical synthesis of improved derivatives led to the identification of active molecules with nanomolar potency and suitable metabolic stability. The mode of action was investigated by diverse methodologies including affinity based protein profiling (AfBPP). For example, one compound stimulates a signal peptidase correlating with enhanced secretion of extracellular proteins. These included essential cell-wall remodeling enzymes whose dysregulation likely explains the associated antibiotic effects.