Aberrant activation of ClpP protease in bacterial and mammalian cells

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Caseinolytic protease P (ClpP) is a highly conserved protease in bacteria and in human mitochondria, which plays an essential role in protein quality control by degrading damaged or misfolded proteins. It has been suggested that ClpP could be an appealing target for developing new antibiotics due to its critical function in bacterial cell division. Small-molecule activators could switch *Staphylococcus aureus* ClpP (*Sa*ClpP) into an uncontrollable state and therefore induces nonselective degradation of essential proteins to force self-digestion of Staphylococcal cells. In addition, aberrant activation of *Homo sapiens* ClpP (*Hs*ClpP) in the mitochondrion could induce degradation of substrates in respiratory chain complex, which led to antitumor effects. However, the development of species-specific activators for certain ClpP protease remains major challenge due to the highly conserved similarity in sequence and protein folding between bacterial and mitochondrional ClpP proteases. We are interested in the development of small-molecule activators with novel chemical scaffolds to selectively target either staphylococcal or mitochondrional ClpP, which would eventually provide novel targeted therapy for cancer and antistaphylococcal agents for bacterial infection as well.

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