In all kingdoms of life, proteases have diverse and often essential physiological roles. The importance of these enzymes in human physiology is reflected in the fact that they are the targets of an estimated 5–10% of all drugs currently in development. Though much of the current drug development is focused on mammalian proteases, their counterparts in bacteria are equally attractive drug targets. The intracellular, self-compartmentalized proteases in bacteria are particularly captivating targets because they are required for viability, virulence factor production and secretion, and coordination of the stress responses that enable survival inside the host. Indeed, several small molecules targeting ClpXP and the 20S proteasome in Mycobacterium tuberculosis are known and are compelling leads for drugs used to treat tuberculosis. It is anticipated that one or more of these molecules targeting intracellular proteases will be desperately needed, “first-in-class” drugs for treating the deadliest bacterial infection.