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DISSERTATION TITLE: *Activation pathways of the class Ib ribonucleotide reductase in Bacillus cereus*

Our body depends on enzymes that ensure optimal performance of cellular processes. One process that is essential to all living organisms is the conversion of ribonucleotides into deoxyribonucleotides – the building blocks of DNA – catalyzed by the enzyme ribonucleotide reductase (RNR). RNR dysfunction can have drastic consequences for cellular activity, and unusually high RNR activity and cell division are common traits of cancer cells. Therefore, RNR studies have been important in the development of cancer drugs.

Pathogenic bacteria also need RNR to survive. Thus, these bacteria could be killed using drugs that target RNR and inhibit its activity. However, RNR enzymes in humans and bacteria are very similar, and knowledge about small differences in their structure and function is important when designing specific, antimicrobial drugs. In her thesis, Marie Lofstad has studied a specific type of RNR (class Ib) in *Bacillus cereus*. These soil bacteria are known to cause food poisoning and for being related to the highly pathogenic anthrax bacteria *Bacillus anthracis*. Class Ib RNR enzymes consist out of two proteins, which together produce building blocks for DNA synthesis and repair. In this PhD work the smallest protein, called NrdF, has been studied using a combined biochemical and biophysical approach.

NrdF is a metalloenzyme, i.e. it requires metals (manganese or iron) to function. The manganese-containing form of NrdF has to be activated by another protein, NrdI, which again is activated by an unknown partner. In this study, Lofstad has identified three proteins in *Bacillus cereus*, so-called flavodoxin reductases (FNRs), which are able to activate NrdI by electron transfer. One of the FNRs, FNR2, works more than ten times faster than the two other proteins, and can activate NrdF together with NrdI. Lofstad and collaborators have also studied the active NrdF enzyme at an electronic level, to elucidate its detailed reaction mechanism. The human RNR enzyme uses iron instead of manganese and does not require NrdI and FNR. Therefore, these results could be important in the development of drugs that inhibit NrdI and FNR and their ability to activate NrdF, without specifically targeting RNR.