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Acetohydroxyacid Synthase: Structure, Function, Regulation and Inhibition

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Acetohydroxyacid synthase is the first enzyme in the branched chain amino acid biosynthesis pathway. It has been the target for herbicides since the 1980s. In total, 58 AHAS inhibitors have been developed into commercial products [1]. This enzyme is only found in plants, bacteria and fungi but not in humans, making it an attractive target not only for herbicide development but also for the discovery of novel antibacterial and antifungal agents [1]. Recently, we have used X-ray crystallography and cryo-EM to solve the first structures of fungal and plant AHAS that include both the regulatory and catalytic subunits [2]. As a result, we can explain for the first time the mechanism of allostery and feedback inhibition for this enzyme. We have also investigated the enzyme as a target for the development of new drugs to treat *Candida albicans* infection. We have shown that mice infected with *C. albicans* recover after treatment with a known plant AHAS inhibitor chlorimuronethyl [3]. Furthermore, we have shown that AHAS inhibitors prevent the growth of *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida auris* and *C. neoformans* in cell susceptibility assays with IC_{50} values as low as 4 nM. In addition, we have determined crystal structures of these compounds in complex with *Candida albicans* AHAS to explain how they bind to the target and to allow for rational structure-based drug discovery. Progress towards the development of AHAS inhibitors as antibacterial and antifungal drugs will be discussed.

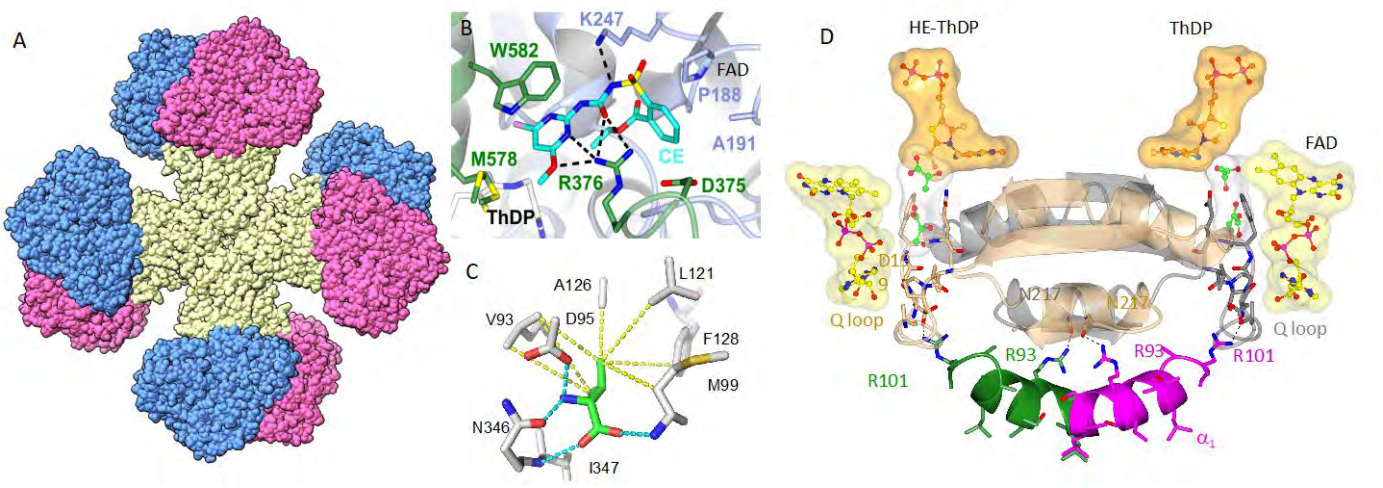

Figure 1. A. Cryo-EM structure of *A.thaliana* AHAS B. The binding of chlorimuronethyl to *C. albicans* AHAS. **C.** The binding of valine to the regulatory subunit of AHAS. **D.** The mechanism for allosteric activation and inhibition of the catalytic subunit by the regulatory subunit of AHAS and by valine.

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