

Poster Presentation

MS53.P45

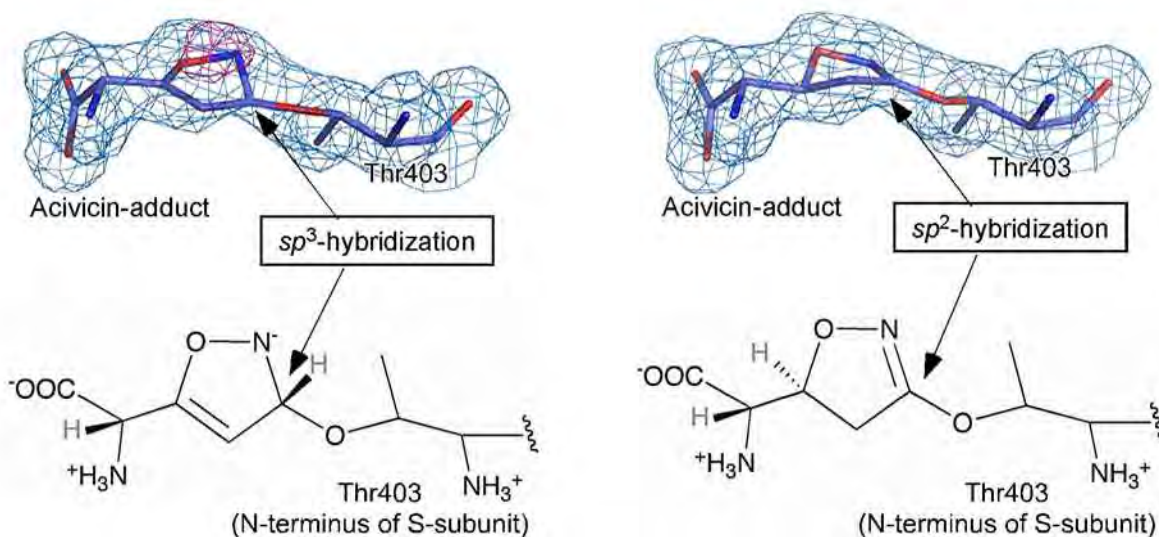
Crystal structures of γ -glutamyltranspeptidase in complex with inhibitors

K. Hirabayashi^{1,2}, T. Ida², C. Li³, H. Suzuki⁴, K. Fukuyama⁵, J. Hiratake³, K. Wada¹

¹University of Miyazaki, Organization for Promotion of Tenure Track, Miyazaki, Japan, ²Osaka University, Department of Biological Sciences, Graduate School of Science, Osaka, Japan, ³Kyoto University, Institute for Chemical Research, Kyoto, Japan, ⁴Kyoto Institute of Technology, Division of Applied Biology, Graduate School of Science and Technology, Kyoto, Japan, ⁵Osaka University, Department of Applied Chemistry, Graduate School of Engineering, Osaka, Japan

γ -Glutamyltranspeptidase (GGT; EC 2.3.2.2) is involved in the degradation of γ -glutamyl compounds such as glutathione (GSH; γ -glutamyl-cysteinyl-glycine). A major physiological role of this enzyme is to cleave the extracellular GSH as a source of cysteine for intracellular glutathione biosynthesis. Another crucial role of GGT is to cleave glutathione-S-conjugates as a key step in detoxification of xenobiotics and drug metabolism. In mammals, GGT has been implicated in physiological disorders such as Parkinson's disease, other neurodegenerative diseases including Alzheimer's disease and cardiovascular disease. The indispensable roles played by GGT in GSH-mediated detoxification and cellular response to oxidative stress suggest that GGT is an attractive pharmaceutical target. We here report the binding mode of acivicin, a well-known glutamine antagonist, to *B. subtilis* GGT at 1.8 Å resolution showing that acivicin is bound to the O γ atom of Thr403, the catalytic nucleophile of the enzyme, through its C3 atom [1]. The observed electron density around the C3 atom was best fitted to the planar and sp² hybridized carbon, consistent with a simple nucleophilic substitution of Cl at the imino carbon by O γ atom of Thr403. Furthermore, comparison of three bacterial enzymes, the GGTs from *E. coli*, *H. pylori* and *B. subtilis* in complex with acivicin, showed significant diversity in the orientation of the dihydroisoxazole ring among three GGTs. The differences are discussed in terms of the recognition of the α -amino and α -carboxy groups in preference to the dihydroisoxazole ring as observed in time-lapse soaking crystal structures of *B. subtilis* GGT with acivicin.

[1] *Acta Crystallogr., Sect.D*, 70, 607-614 (2014)



Keywords: glutathione, acivicin, Ntn-hydrolase family