28AB-ISMS31 **Discovery of Novel ITK Type 1½ Inhibitors Using Fragment-based Drug Design**

○Sae JIKIHARA[1], Takahiko YAMAMOTO[1], Kazuya YASUO[1], Maki HATTORI[1], Eriko MATSUOKA[1], Chiaki FUJIKOSHI[1], Kazuya KANO[1], Morio NAGIRA[1], Satoru ISHIDA[1], Ichiro HIKITA[1], Ken-ichi MATSUMURA[1], Hiroto YAMAGUCHI[1], Kenichi HIGASHINO[1]
[1]Shionogi & Co., Ltd.

Interleukin-2 inducible tyrosine kinase (Itk) is a member of the Tec family tyrosine kinases. Its signaling pathway plays an important role in the activation and differentiation of T-cells. Therefore, inhibition of Itk is considered to be a novel therapeutic strategy for allergic diseases. Our lead compound was found to be categorized into type-1½ inhibitor, characterized by DFG-in conformation of the activation loop. To improve its low Lck selectivity, we planned to switch the hinge binding motif using FBDD fragment-linking approach, while keeping its valuable back pocket binding motif, pyrazolone analogue. As a result, we could obtain a novel inhibitor with high Itk/Lck selectivity. The details of fragment screening, X-ray complex structures of fragments and compounds, process of fragment-linking and SAR will be discussed.

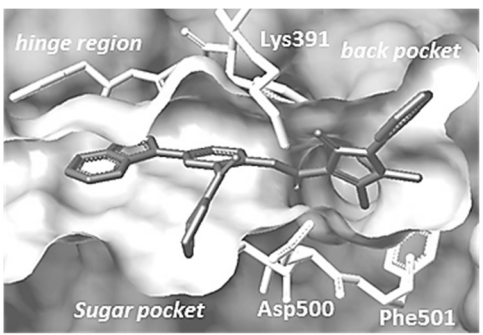

Figure: Xray structure of **new inhibitor**