[P22] In silico identification of novel inhibitors of S6K1 kinase by SBDD and LBDD approach

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S6K1 is the member of the serine-threonine kinase family and phosphorylates 70S ribosomal protein S6. Because S6K1 plays important roles in metabolism, cell growth, and overexpresses at renal cell carcinoma and breast cancer cells, S6K1 is expected to be a potential new target of anticancer agent. To find novel scaffolds as S6K1 kinase inhibitors, we demonstrated two strategies of in silico screening and inhibition assay of S6K1 kinase supported with X-ray crystal structure analysis.

At the first round of in silico screening, we selected the screening compound sets by structure-based drug design (SBDD) and ligand-based drug design (LBDD). We demonstrated an efficient in silico screening based on k-PALLAS [1], which is the semi-automatic optimization system of docking conditions developed by Honma and co-workers at RIKEN. In parallel with the docking simulations, 3D similarity searches were performed using the shape-comparison program ROCS (Rapid Overlay of Chemical Structures), followed by the kinase mobility shift assay. Known S6K1 ligands and S6K1 X-ray ligands were used as queries for the 3D similarity searches. In the second round of in silico screening, 2D similarity searches were performed by using the 23 hits with IC_{50} < 10 μM as queries, identified in the first round in silico screening. Compound library which were used for the first and second rounds, are supplied by Open Innovation Center for Drug Discovery at the University of Tokyo.

After the kinase mobility shift assay, five and four compounds with IC_{50} <= 500 nM, were obtained from the first and second rounds respectively. Furthermore, we succeeded in getting five X-ray complex structures of S6K1 and the hit compounds [2]. From docking simulation approach with k-PALLAS, we acquired the novel scaffold of S6K inhibitors which are different from known S6K1 ligands so far.

In this poster session, we will discuss our in silico approach to identify of new scaffolds of S6K1 inhibitors.

Bibliography:

[1] T.Sato; H.Watanabe; K.Tsuganezawa; H.Yuki; J.Mikuni; S.Yoshikawa; M.Kukimoto-Niino; T.Fujimoto; Y.Terazawa; M.Wakiyama; H.Kojima; T.Okabe; T.Nagano; M.Shirouzu; S.Yokoyama; A.Tanaka; T.Honma. Bioorg Med Chem. 20(2012) 3756-3767.
[2] H.Niwa; J.Mikuni; S.Sasaki; Y.Tomabechi; K.Honda; M.Ikeda ; N.Ohsawa; M.Wakiyama; N.Handa; M.Shirouzu; T.Honma; A.Tanaka; S.Yokoyama. J. Struct Funct Genomics. 15 (2014) 153-164.