OS04-5 **Chemical biology of calyculin A**

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Calyculin A is the potent protein phosphatases (PP1 & 2A) inhibitor isolated from marine sponge *Discodermia calyx*. Its unique structure is composed of hybrid units derived from PKS and NRPS. The structure and activity relationship study with natural and semi-synthetic derivatives disclosed the functional groups and partial structures essential for either enzyme inhibition or cytotoxicity. As a results polyketide unit is essential for both enzyme inhibition and cytotoxicity, whereas peptide portion takes part in only cytotoxicity. The SAR data motivated us to construct the chemical library based on the calyculin pharmacophore in order to develop selective inhibitors against PP subtypes including PP1, 2A and 2B. Subtype selective inhibitors would be useful chemical probe to elucidate the signal transduction mechanism by phosphorylation known to be one of the major post translational modification.

Finally, cloning of the biosynthetic gene cluster of calyculin A from sponge metagenomic DNA library will also be discussed. Even though the real producing organisms of marine natural products are hardly cultivable, the metagomic approach would allow for identification of their biosynthetic gene clusters.