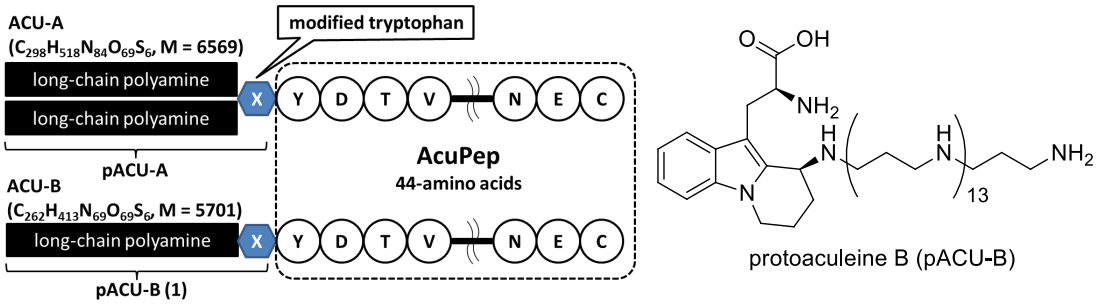
Studies on Synthesis and Evaluation of Peptide–Polyamine Conjugate from Marine Origin

(*Graduate School of Nanobioscience, Yokohama City University*)
Masayoshi Miyahara, ○Raku Irie, Masato Oikawa
Keywords: Peptide; Polyamine; Aculeine; Hemolysis; Cytotoxicity

Aculeines (ACUs) are modified peptide toxins isolated from the marine sponge *Axinyssa aculeata*.[1] ACU-A and -B are comprised of a common 44- amino acid ribosomal peptide (AcuPep) conjugated with modified tryptophan residues named protoaculeines (pACUs). Protoaculeine B is composed of a tryptophan-derived heterotricycle and a long-chain polyamine (LCPA) that is a linearly extended 14-mer of 1,3-propanediamine.[2]



ACUs are toxic to various mammalian cells and show pro-convulsant activity in mice. The mechanism of these discrete actions stems from their ability to disrupt cell membranes through the unique interaction between ACUs and the plasma membrane.

In order to further investigate the detailed mechanism of action of ACUs, we embarked on synthesis of pACU-B directed toward chemical synthesis of ACUs, various analogues, and model compounds. In the last annual meeting, we have reported our successful synthesis of differently protected 12-mer of 1,3-propanediamine by employing the new strategy.[3] Herein, we report preparation of the fully protected minor homolog of pACU-B with 12-mer polyamine,[4] and the bioactivity of the unprotected core amino acid.

[1] S. Matsunaga, M. Jimbo, M. B. Gill, L. L. Lash-Van Wyhe, M. Murata, K. Nonomura, G. T. Swanson, R. Sakai, *ChemBioChem* **2011**, *12*, 2191.
[2] S. Matsunaga, R. Kishi, K. Otsuka, M. J. Fujita, M. Oikawa, R. Sakai, *Org. Lett.* **2014**, *16*, 3090.
[3] (a) M. Miyahara, H. Shiozaki, Y. Ishikawa, M. Oikawa, *The 98th CSJ Annual Meeting*, **2018**, 1D2-19. (b) M. Miyahara, H. Shiozaki, H. Tukada, Y. Ishikawa, M. Oikawa, *Tetrahedron Lett.* **2018**, *59*, 4197.
[4] H. Shiozaki, M. Miyahara, K. Otsuka, K. Miyako, A. Honda, Y. Takasaki, S. Takamizawa, H. Tukada, Y. Ishikawa, R. Sakai, M. Oikawa, *Org. Lett.* **2018**, *20*, 3403.