02-4

Visualized and quantitative structural analysis of peptidomimetics for PPI drug discovery

Hajime Takashima[1] takashima@prismbiolab.com
Atsushi Yoshimori[2] yoshimori@itmol.com
Eiji Honda[1] honda@prismbiolab.com
Tomonori Taguri[1] taguri@prismbiolab.com
Jun Ozawa[1] ozawa@prismbiolab.com
Satoshi Shuto[3] shu@pharm.hokudai.ac.jp
Shunji Suetaka[4] shunji-suetaka@g.ecc.u-tokyo.ac.jp
Nao Sato[4] sato-nao140@g.ecc.u-tokyo.ac.jp
Yuuki Hayashi[4] hayashi@bio.c.u-tokyo.ac.jp
Munehito Arai[4,5] arai@bio.c.u-tokyo.ac.jp
Dai Takehara[1] takehara@prismbiolab.com

[1] PRISM BioLab Co., Ltd., 2-26-1 Muraoka-Higashi, Fujisawa, Kanagawa, 251-0012, Japan
[2] Institute for Theoretical Medicine, Inc., 2-26-1 Muraoka-Higashi, Fujisawa, Kanagawa, 251-0012, Japan
[3] Faculty of Pharmaceutical Science, Hokkaido University 160-8582, Kita 8, Nishi 5, Kita-ku, Sapporo, Hokkaido, 060-0808, Japan
[4] Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Meguro, Komaba, Tokyo 153-8902, Japan
[5] Department of Physics, Graduate School of Science, The University of Tokyo, 3-8-1 Meguro, Komaba, Tokyo 153-8902, Japan

Keywords: Peptidomimetics, Conformational analysis, PepMetics™ Library, PPIs

Protein–protein interactions (PPIs) are significant drug targets and many peptidomimetic molecules have been developed for modulating PPIs [1]. Nevertheless, no analytical method has been established to evaluate how precisely these molecules can mimic target peptide structures.

We developed new methods which enable visual, comprehensive, and quantitative analysis of three-dimensional structures of peptidomimetics: peptide conformation distribution (PCD) plot and peptidomimetic analysis (PMA) map [2]. These methods are based on the conformational analysis of multiple side-chain C_α-C_β bonds of a peptide fragment and their corresponding bonds (pseudo-C_α-C_β bonds) in a peptidomimetic molecule, instead of the Ramachandran plot [3] using φ and ψ angles of a single amino acid. PCD-plot is an alignment-free method and visually clarifies conformation distribution of peptidomimetic molecules in the chemical space and similarity with its target peptide secondary structures. PMA-map is an alignment-based method and can quantitatively evaluate similarity between various types of peptidomimetic molecules and their target peptide structures.

Results obtained from analysis using these two methods indicated that our PepMetics™ scaffold, multi-facial α-helix mimetics, is an excellent peptidomimetics that can mimic spatial positioning of the side-chains of α-helix precisely. We have developed a peptidomimetic compound library (PepMetics™ Library) using our PepMetics™ scaffolds and have found PPI hit compounds for the interactions of KIX and c-Myb/MLL proteins known as targets for cancer and leukemia.

In summary, our methods and strategies are useful for development of new peptidomimetic molecules and rational PPI drug discovery.

[1] Milroy, L. G.; *et al.*, Modulators of protein-protein interactions, *Chem. Rev.*, **2014**, 114, 4695-4748.
[2] Takashima, H.; Yoshimori, A.; *et al.*, Visualized and quantitative conformational analysis of peptidomimetics, submitted.
[3] Ramachandran, G. N.; *et al.*, Stereochemistry of polypeptide chain configurations, *J. Mol. Biol.*, **1963**, 7, 95–99.