SL21

Multi-Template Method and Dramatype Method for Seeds Generation

Yuichi Hashimoto

Institute of Molecular & Cellular Biosciences, The University of Tokyo

Multi-template method:

The number of proteins with different amino acid sequences which are of biological interest and/or which can be drug targets is enormous. The number of human proteins with unique sequences is estimated to be 50,000-70,000. Although the number of human proteins is enormous from the standpoint of amino acid sequences, the spatial structure of the proteins ignoring the chemical nature (denoted as “fold structure”) is thought to be far more conserved in evolution than amino acid sequence. The number of “fold structure” types characteristic for all domains occurring in human proteins is thought to be fairly limited to approximately 1,000. Therefore, assuming one “fold structure” being distributed evenly in all human proteins (*i.e.*, 50-70 human proteins), and when one focuses on only spatial structure ignoring physical/chemical interactions, one might expect that unique template/scaffold structure which spatially fits one “fold structure” can be a “multi-template” for structural development of “ligands” for 50-70 human proteins. The structures of ligands that bind to one member of the “fold structures” may be used for the development of novel ligands for other members of the same “fold structure” . Application of steroid substitutes (including diphenylmethane and diphenylethane skeletons) and thalidomide as multi-templates resulted in creation of various kinds of biologically active compounds.

Dramatype method:

Chemical control of protein function/localization/recruitment is associated with normal or abnormal folding induced by binding of small chemicals. Abnormal folding of specific proteins has been known to cause various diseases, including retinitis pigmentosa. Therefore, dynamic folding of proteins can be target phenomena for seeds generation. Based on this idea, various biologically active compounds, including nuclear receptor antagonists (helix 12 folding-inhibition hypothesis), regulators of mutated rhodopsin cellular location (normalization of trafficking) and decomposition inducers of CRABP (utilization of masked ubiquitin-ligase activity), etc., have been created.