【Grant-in-Aid for Specially Promoted Research】

Science and Engineering

Title of Project： Challenges to the remaining issues of therapeutically valuable pseudo-natural peptides and products

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Research Project Number: 20H05618 Researcher Number：00361668
Keyword：nonstandard peptide, pseudo-natural products, mid-sized molecules, drug discovery

【Purpose and Background of the Research】

The ultimate goal of this project is to establish an empirical guidance how membrane permeable mid-sized molecules on the basis of macrocyclic peptides and pseud-natural products could be discovered and developed. The RaPID (Random non-standard Peptides Integrated Discovery) system devised by this PI revolutionized the discovery process of de novo bioactive "nonstandard" macrocyclic peptides that are peptidase-resistance, potent binding to target proteins in the order of nM–pM range, and occasionally cell membrane permeable; however, it has yet a remaining issue of the reliability to devise the highly cell membrane and small intestine permeable, *i.e.* oral available, molecules. To establish the guidance for devising such mid-sized molecules, similar to "Lipinski's rule of five", two critical experimental data must be accumulated. First, we need to have a method to reasonably predict the cell membrane permeability and ideally also small intestine permeability. Second, to establish such a method, we need to have more examples for cell membrane permeable and non-permeable peptides where their structures are somewhat similar.

【Research Methods】

The PI has proposed four specific aims that challenge the remaining issues of this topic as follows.

① Establishing the empirical guidance of membrane permeable peptides and pseudo-natural products
② RaPID display of cyclic β-, cyclic γ-, and unsaturated cyclic amino acids-containing (exotic) peptide libraries and selection of active species
③ RaPID display of pseudo-natural products generated by post-translational modifying enzymes and selection of active species
④ Studies on cell membrane and Caco-2 permeability of exotic peptides and pseudo-natural products

We will design and execute the experiments based on the above specific aims, and challenge the unsolved issues.

【Expected Research Achievements and Scientific Significance】

This project will be executed by a feedback cycle of experimental plans as follows: We execute the specific aim ① based on our currently available cell membrane permeable and non-permeable peptides; execute the specific aims ② and ③ to build "smart" libraries to obtain potent binders against intracellular target proteins of interest; and test them for cell membrane permeabilities in the specific aim ④; the data will be feedback to the specific aim ① to increase our knowledge of structure-activity relationships, and the knowledge will be fed to the design of "smarter" libraries of ② and ③, followed by ④ including small intestine permeability of active species. We expect that such collective data and knowledge will lead us to a useful guidance and possibly "a rule" for accessing desired mid-sized molecules faster and more reliably.

【Publications Relevant to the Project】

• Ribosomal synthesis and de novo discovery of bioactive foldamer peptides containing cyclic β-amino acids; T. Katoh; T. Sengoku; K. Hirata; K. Ogata; H. Suga* **Nature Chemistry,** (2020) DOI: 10.1038/s41557-020-0525-1
• Promiscuous enzymes cooperate at the substrate level en route to lactazole A; A.A. Vinogradov; M. Shimomura; N. Kano; Y. Goto; H. Onaka, H. Suga* **Journal of the American Chemical Society,** in press (2020) DOI: 10.1021/jacs.0c05541
• Introduction to Thiopeptides: Biological Activity, Biosynthesis, and Strategies for Functional Reprogramming; A.A. Vinogradov; H. Suga* **Cell Chemical Biology,** Accepted article (2020) DOI: 10.1016/j.chembiol.2020.07.003
• Ribosomal Elongation of Cyclic γ-Amino Acids using a Reprogrammed Genetic Code; T. Katoh; H. Suga* **Journal of American Chemical Society**, 142, 4965-4969 (2020) DOI: 10.1021/jacs.9b12280

【Term of Project】 FY2020-2024

【Budget Allocation】 485,800 Thousand Yen

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