

## 【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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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 pseudo-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  $\beta$ -, cyclic  $\gamma$ -, 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  $\beta$ -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  $\gamma$ -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

#### 【Homepage Address and Other Contact Information】

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