ELUCIDATION OF LIFE PHENOMENA BY ORGANIC CHEMISTRY

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An organic chemical approach such as synthesis and spectroscopy is quite useful for elucidating various life phenomena. It is most important to identify bioactive compounds and study their mechanism of action in the area of organic chemistry in life science. Our current research mainly focuses on cancer therapeutics, tumor promoters, prevention and therapeutics of Alzheimer's disease by functional foods, antibody, and DNA/RNA aptamers.

Synthesis and Antibody Development of Amyloid β Oligomers

Structure of the aggregates (oligomers) of 42mer amyloid β -protein (A β 42) involved in Alzheimer's disease (AD) is analyzed by NMR, IM-MS and X-ray crystallography. Based on the obtained data, antibodies that are specific to the toxic oligomers of A β 42 are being developed for diagnostic and therapeutic uses.



Prevention of Alzheimer's Disease and Its Mode of Action

Inhibition of aggregation of A β 42 by functional food and traditional herb is promising for AD prevention. Based on NMR and LC-MS analyses, it was found that catechol-type flavonoids could form Michael adducts with Lys residues within β -sheet region, resulting in suppression of aggregation. Furthermore, their pharmacokinetic analyses including brains and intestinal tracts in AD model mice are underway.



Development of Bryostatin-Type Anticancer Drugs

Bryostatin 1 is currently undergoing clinical trials for the treatment of cancer. However, its limited availability from natural sources and difficulty in the synthesis hamper further studies on its mode of action and structural optimization. We found a simple analog (aplog-1) of the tumor-promoting aplysiatoxin to become another therapeutic lead for cancer. The structural optimization and elucidation of its mode of action is underway.



Development of Functional DNA/RNA Oligonucleotides

DNA/RNA aptamers have potent affinity and selectivity against target peptides and proteins comparable to monoclonal antibodies. Using vitro selection (SELEX: systematic in evolution of ligands by exponential enrichment), RNA aptamers against toxic oligomers of Aβ42 are being developed for early diagnosis of



Key words

Alzheimer's disease, β -amyloid, peptide, tumor promoter, cancer, inflammation, protein kinase C, functional food, pharmacokinetics, aptamer, oligonucleotide

Recent publications

A Toxic Conformer of A β 42 with a Turn at 22-23 is a Novel Therapeutic Target for Alzheimer's Disease

Izuo N, Kasahara C, Murakami K, Kume T, Maeda M, Irie K, Yokote K, Shimizu T (2017) Sci Rep 7: 11811

Loss of the Phenolic Hydroxyl Group and Aromaticity from the Side Chain of Antiproliferative 10-Methyl-aplog-1, a Simplified Analog of Aplysiatoxin, Enhances Its Tumor-promoting and Proinflammatory Activities

Hanaki Y, Kikumori M, Tokuda H, Okamura M, Dan S, Adachi N, Saito N, Yanagita RC, Irie K (2017) Molecules 22: 631

Synthetic Models of Quasi-stable Amyloid β40 Oligomers with Significant Neurotoxicity

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Semisynthesis and Structure-activity Studies of Uncarinic Acid C Isolated from *Uncaria rhynchophilla* as a Specific Inhibitor of the Nucleation Phase in Amyloid β42 Aggregation

Yoshioka T, Murakami K, Ido K, Hanaki M, Yamaguchi K, Midorikawa S, Taniwaki S, Gunji H, Irie, K (2016) J Nat Prod 79: 2521-2529

Binding Mode Prediction of Aplysiatoxin, a Potent Agonist of Protein Kinase C, through Molecular Simulation and Structure-activity Study on Simplified Analogs of the Receptor-Recognition Domain

Ashida Y, Yanagita RC, Takahashi C, Kawanami Y, Irie K (2016) Bioorg Med Chem 24: 4218-4227

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Kikumori M, Yanagita RC, Tokuda H, Suenaga K, Nagai H, Irie K (2016) Biosci Biotechnol Biochem 80: 221-231

Structural Insights into Mechanisms for Inhibiting Amyloid β42 Aggregation by Non-catechol-type Flavonoids

Hanaki M, Murakami K, Akagi K, Irie K (2016) Bioorg Med Chem 24: 304-313