Japan Academy Prize to:

Hiroshi OHRUI
Professor, Yokohama College of Pharmacy
Professor Emeritus, Tohoku University

and

Takeshi KITAHARA
Professor, Faculty of Pharmaceutical Science, Teikyo-Heisei University
Guest Professor, Kitasato University
Professor Emeritus, The University of Tokyo

for "Invention and Application of Molecules with Novel Biological Functions"

Outline of the work:

Studies on the synthesis of natural products and related substances with remarkable biological activities can play a key role to develop not only basic research for investigating biological phenomena but also practical applications through the synthesis of novel bioactive molecules.

From this standpoint, Drs. Hiroshi Ohrui and Takeshi Kitahara synthesized novel compounds with biological functions by rational synthetic design and utilized them for frontier researches in biological sciences.

Achievements are summarized as follows:

1. Development of supersensitive methods of analysis and their applications

It was impossible to differentiate asymmetric centers separated farther than four or more atoms until recently. Dr. Hiroshi Ohrui developed extremely effective method to analyze remote asymmetric centers by inventing novel carbohydrate reagents with high performance based on his discovery of the gauche effect between oxygen atoms in carbohydrates. These reagents made possible to separate even eight stereoisomers of tocopherol clearly at the concentration of femtomole level using HPLC for the first time in the world. Establishment of this revolutionarily effective method of analysis by new concept should contribute to solve a lot of difficult problems in the field of biological sciences as well as in analytical chemistry.

He also invented the fluorescent reagent, diphenyl-1-pyrenylphosphine, which enabled to establish efficient quantitative analysis of active oxygen and/or superoxide in the living body with high sensitivity.

2. Invention of a useful molecule for organic synthesis and of insecticides for practical applications

Dr. Takeshi Kitahara invented an extremely useful diene, 1-methoxy-3-trimethylsiloxy-1,3-butadiene with

extraordinarily high reactivity in the Diels-Alder reaction for the synthesis of alicyclic compounds. Many biologically active natural products have successfully been synthesized employing the diene including vernolepin, vernomenin and damascones. The diene, so-called the Danishefsky-Kitahara Diene, was proved to be an extremely versatile regent to give multifunctional cyclic compounds, especially carbohydrates and other heterocycles with important biological functions, and therefore has been utilized worldwide over the years.

He also discovered for the first time an acid moiety of pyrethroids with effective insecticidal activity, 1,1,2,2-tetramethylcyclopropanecarboxylic acid (tetramethyl acid), and succeeded in invention of a domestic insecticide, Terarethrin (Knockthrin®) through an extensive study on structure-activity relationship (SAR study). This discovery deeply influenced to the world of pesticide science and culminated in the development of synthetic pyrethroids as agrochemcals. In fact, using tetramethyl acid itself, one of the most effective and safe agricultural insecticides, Fenpropathrin (Danitol®), has been manufactured in several hundred tons a year and used worldwide.

3. Synthesis of useful bioactive molecules and their applications

They synthesized a number of bioactive substances to develop remarkable biological functions and their applications.

Dr. Kitahara succeeded in simple and efficient synthesis of mugineic acid congeners, active phytosiderophores, and discovered important results on iron-absorption in plants by collaboration with plant physiologists. Worldwide supply of those samples of phytosiderophores has enabled to study extensively the physiology of iron-absorption.

He also synthesized various inhibitors against cell-cycle propagation and by collaborations with biochemists, remarkable biological functions of those inhibitors have been disclosed. For example, he found a synthetic analog, spliceostatin, with much higher activity than that of an anticancer inhibitor, FR901464, from detailed SAR study. Through identification of target proteins followed by precise functional analysis, spliceostain was shown to be the first example of the anticancer agent which suppresses to form normal proteins by inhibition of the splicing from pre-mRNA to mRNA.

Dr. Ohrui initiated “chiral pool strategy” by employing carbohydrates as substrates to give chiral materials, succeeded in the synthesis of a number of bioactive substances including aminoglycosides and nucleosides, and invented low toxic Anti-HIV nucleosides by rational design.

In summary, they synthesized numerous novel molecules with remarkable biological functions, which contributed to develop wide areas of analytical chemistry, organic chemistry, plant physiology and life sciences by worldwide collaborations.

Through these achievements, Dr. Ohrui has received the Award of the Japan Society of Analytical Chemistry, Japan Prize of Agricultural Science and the Yomiuri Agricultural Prize. Dr. Kitahara has received the Award of the Society of Synthetic Organic Chemistry, Japan, Japan Prize of Agricultural Science and the Yomiuri Agricultural Prize.

Major publications by Dr. H. Ohrui

1. H. Kuzuhara, H. Ohrui and S. Emoto, Total Synthesis of Polyoxin J, *Tetrahedron Lett*., 5005–5009 (1973).
2. H. Ohrui and S. Emoto, Stereospecific Synthesis of (+)-Biotin, *Tetrahedron Lett*., 3657–3661 (1976).
3. H. Ohrui, Y. Nishida, M. Watanabe, H. Hori and H. Meguro, ^{1}H-NMR Studies on (6*R*)- and (6*S*)-Deuterated (1-6)-Linked Disaccharides, Assignment of the Preferred Rotamers about C5-C6 Bond of (1-6)-Disaccharides in Solution, *Tetrahedron Lett*., **26**, 3251–3254 (1985).
4. K. Akasaka, T. Suzuki, H. Ohrui and H. Meguro, Study on Aromatic Phosphines for Novel Fluorometry of Hydroperoxides, Synthesis and Spectral Properties of Diphenyl Aryl Phosphines and Their Oxides, *Anal*. *Lett*., **20**, 731–745 (1987).

5. K. Akasaka, H. Meguro and H. Ohrui, Enantiomeric Separation of Carboxylic Acids Having Chiral Centers Remote from the Carboxyl Group by Labeling with a Chiral Fluorescent Derivatization Reagent, *Tetrahedron Lett*., **38**, 6853–6856 (1997).
6. K. Akasaka and H. Ohrui, Enantiomeric Separation of Branched Fatty Acids after Conversion with *trans*-2-(2,3-Anthracenedicarboximido)cyclohexanol, a Highly Sensitive Chiral Fluorescent Conversion Reagent, *Biosci*. *Biotechnol*. *Biochem*., **63**, 1209–1215 (1999).
7. K. Akasaka and H. Ohrui, Development of Phosphine Reagents for the High-Performance Liquid Chromatographic Fluorometric Determination of Lipid Hydroperoxides, *J*. *Chromatog*. *A*, **881**, 159–170 (2000).
8. H. Ohrui, S. Kohgo, K. Kitano, S. Sakata, E. Kodama, K. Yoshimura, M. Matsuoka, S. Shigeta and H. Mitsuya, Synthesis of 4'-*C*-Ethynyl-*β*-D-*arabino*- and 4'-*C*-Ethynyl-*β*-D-*ribo*-pentofuranosylpyrimidines and purines and Evaluation of Their Anti-HIV Activity, *J*. *Med*. *Chem*., **43**, 4516–4525 (2000).
9. E. Kodama, S. Kohgo, K. Kitano, H. Machida, H. Gatanaga, S. Shigeta, M. Matsuoka, H. Ohrui and H. Mitsuya, 4'-*C*-Ethynyl Nucleoside Analogs: Potent Inhibitors of Multidrug-resistant Human Immunodeficiency Virus In Vitro, *Antimicrobial Agents and Chemotherapy*, **45**, 1539–1546 (2001).
10. T. Tashiro, K. Akasaka, H. Ohrui, E. Fattorusso and K. Mori, Determination of the Absolute Configuration at the Two Cyclopropane Moieties of Plakoside A, an Immunosuppressive Marine Galactosphingolipid, *Eur*. *J*. *Org*. *Chem*., 3659–3665 (2002).
11. H. Ohrui, A Pioneering Study in Agricultural Sciences and Bioorganic Chemistry, *Nippon Nougeikagaku Kaishi*, **78**, 1050–1055 (2004).
12. H. Ohrui, R. Kato, T. Kodaira, H. Shimizu, K. Akasaka and T. Kitahara, Development of Highly Potent D-Glucosamine-Based Chiral Fluorescent Labeling Reagents and a Microwave-Assisted Selective Glycosidation of Methyl Glycoside Reagent, *Biosci*. *Biotechnol*. *Biochem*., **69**, 1054–1057 (2005).
13. H. Ohrui, 2'-Deoxy-4'-*C*-Ethynyl-2-Fluoroadenosine, a Nucleoside Reverse Transcriptase Inhibitor, is Highly Potent against All Human Immunodeficiency Viruses Type 1 and has Low Toxicity, *The Chemical Record*, **6**, 133–143 (2006).
14. H. Ohrui, Development of Highly Potent Chiral Discrimination Methods that Solve the Problems of the Diastereomer Method, *Proc*. *Jpn*. *Acad*. *Ser*. *B*, **83**, 127–135 (2007).

Major publications by Dr. T. Kitahara

1. M. Matsui and T. Kitahara, Study on Chrysanthemic Acid Part XVIII. A New Biologically Active Component Related to Chrysanthemic Acid, *Agric*. *Biol*. *Chem*., **31**, 1143–1150 (1967).
2. T. Kitahara, K. Fujimoto and M. Matsui, The Synthesis of 2,2-Dimethyl-3,3-dichlorocyclopropanecarboxylic Acid, a Novel Active Acid Moiety of Pyrethroids, *Agric*. *Biol*. *Chem*., **38**, 1511–1514 (1974).
3. S. Danishefsky and T. Kitahara, A Useful Diene for the Diels-Alder Reaction, *J*. *Am*. *Chem*. *Soc*., **96**, 7807–7808 (1974).
4. S. Danishefsky, T. Kitahara, P. F. Schuda and S. J. Etheredge, A Remarkable Epoxide Opening. An Expeditious Synthesis of Vernolepin and Vernomenin, *J*. *Am*. *Chem*. *Soc*., **98**, 3028–3030 (1976).
5. T. Kitahara, M. Mori and K. Mori, Total Synthesis of (−)-Periplanone-B, Natural Major Sex-Excitant Pheromone of the American Cockroach, *Periplaneta americana*, *Tetrahedron*, **43**, 2689–2699 (1987).
6. T. Kitahara, Chiral Synthesis of Natural Products as Semiochemicals and Bioregulators, *Studies in Natural Product Chemistry*, Vol. 6, pp. 537–566 (1990). A.-ur-Rahman ed., Elsevier Internatl. Sci., Amsterdam.
7. T. Kitahara, T. Nishi and K. Mori, Synthesis of Both the Enantiomers of Methyl Epijasmonate, *Tetrahedron*, **47**, 6999–7006 (1991).
8. S. S. Klair, H. R. Mohan and T. Kitahara, A Novel Synthetic Approach towards Phytosiderophores: Expeditious

Synthesis of Nicotianamine and 2'-Deoxymugineic Acid, *Tetrahedron Lett*., **39**, 89–92 (1998).

9. T. Kitahara and H. Watanabe, Enantioselective Synthesis of Bioactive Molecules Related to Plant Protection, *J*. *Synth*. *Org*. *Chem*., *Jpn*., **56**, 884–895 (1998).
10. H. Watanabe, H. Watanabe and T. Kitahara, Total Synthesis of (−)-Pironetin, *Tetrahedron Lett*., **39**, 8313–8316 (1998).
11. S. W. Ki, K. Ishigami, T. Kitahara, K. Kasahara, M. Yoshida and S. Horinouchi, Radicicol Binds and Inhibits Mammalian ATP Citrase Lyase, *J*. *Biol*. *Chem*., **275**, 39231–39236 (2000).
12. G. Schaaf, U. Ludewig, B. E. Erenoglu, S. Mori, T. Kitahara and N. von Wiren, ZmYS1 Functions as a Proton-Coupled Symporter for Phytosiderophore- and Nicotianamine-Chelated Metals, *J*. *Biol*. *Chem*., **279**, 9091–9096 (2004).
13. T. Kitahara, Synthetic Studies on Natural Products with Remarkable Biological Activities. *Nippon Nougeikagaku Kaishi*, **78**, 460–469 (2004).
14. D. Kaida, H. Motoyoshi, E. Tashiro, T. Nojima, M. Hagiwara, K. Ishigami, H. Watanabe, T. Kitahara, T. Yoshida, H. Nakajima, T. Tani, S. Horinouchi and M. Yoshida, Spliceostatin A Targets SF3b and Inhibits Both Splicing and Nuclear Retention of Pre-mRNA, *Nature Chem*. *Biol*., **3**, 576–583 (2007).