

The Nakanishi Symposium

on Natural Products & Bioorganic Chemistry

Doshisha University

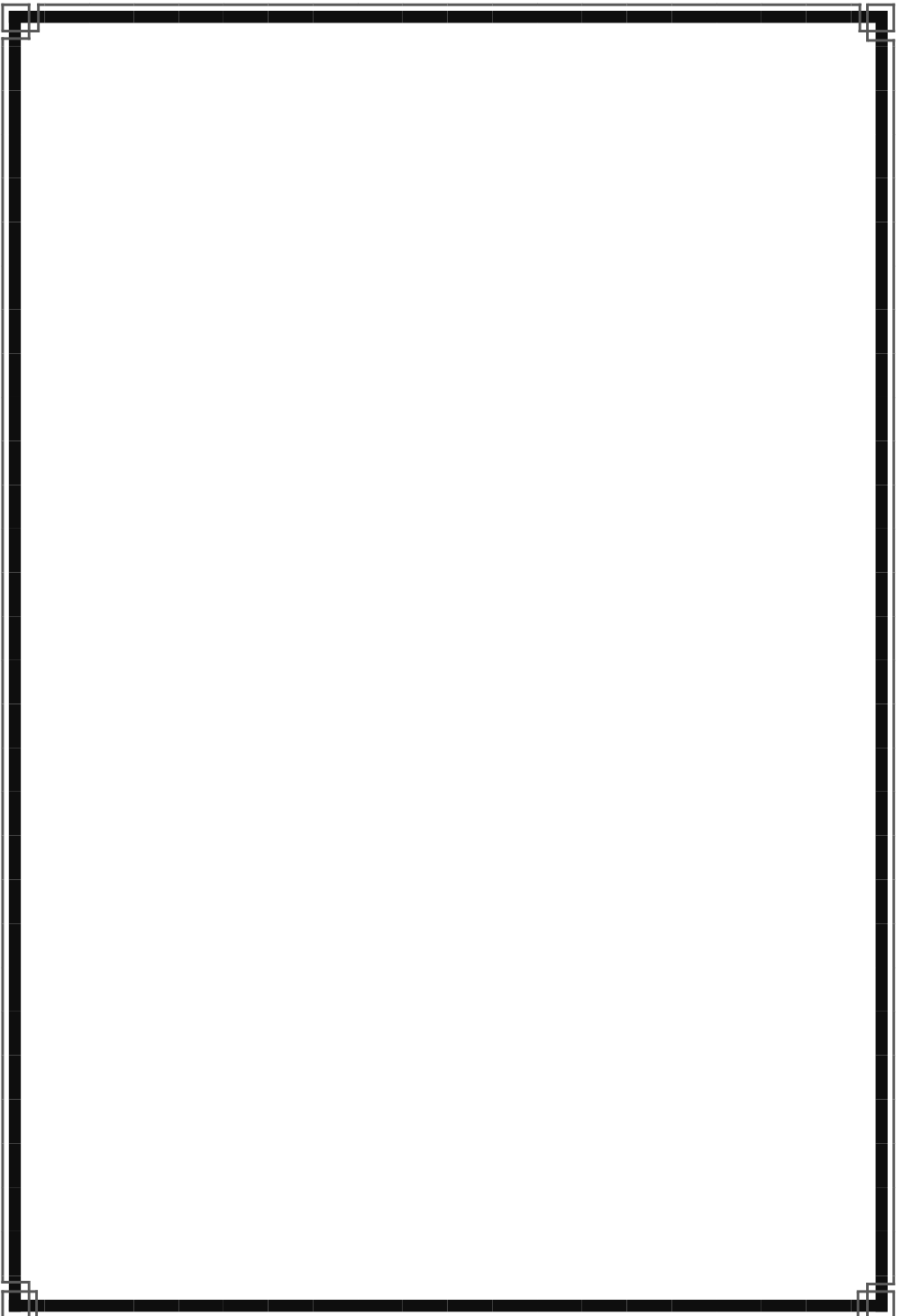
March 24, 2016

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Kusumoto, Shoichi
Professor Emeritus, Osaka University

■EDUCATION

B.Sc. Chemistry, Faculty of Science, Osaka University 1963
Ph. D. Organic Chemistry, Osaka University 1969

■ACADEMIC CAREER

Osaka City University 1964 – 1969, 1971 - 1972
Research Associate, Inst. of Organic Chemistry, Faculty of Science
German Cancer Research Center, Heidelberg 1969 - 1971
Research Fellow of Alexander von Humboldt-Foundation
Osaka University 1972 - 2004
Department of Chemistry, Graduate School of Science
Research Associate, Associate Professor, then Professor of Organic
Chemistry
Suntory Institute for Bioorganic Research 2004 - 2011
Research Director

■RESEARCH TOPICS

- Synthesis of immunostimulatory bacterial peptidoglycan partial structures
- Structure, synthesis and biological functions of bacterial endotoxin
- Synthetic strategies for glycoconjugates: versatile protecting groups and efficient glycosylation

■SELECTED PUBLICATIONS

1. Key structures of bacterial peptidoglycan and lipopolysaccharide triggering the innate immune system of higher animals: Chemical synthesis and functional studies. S. Kusumoto, K. Fukase, T. Shiba, Proc. Japan Acad. Ser. B, 2010, 86 (4), 322-337.
2. Synthesis of endotoxic principle of bacterial lipopolysaccharide and its recognition by the innate immune systems of hosts. S. Kusumoto, K. Fukase, Chem. Rec., 2006; 6:333-343.
3. Synthesis of Lipopolysaccharide, Peptidoglycan, and Lipoteichoic Acid Fragments. S. Kusumoto, K. Fukase, Y. Fujimoto, "Comprehensive Glycoscience", Vol. 1, Ed J.P. Kammeling, Elsevier (Amsterdam 2007), pp. 685-711.
4. Synthesis of glycolipids. S. Kusumoto, M. Oikawa, "Glycoscience III", eds. B. F-Reid, K. Tatsuta, and J. Thiem, Springer (Berlin, 2001), pp. 2107-2148.

■AWARDS

- Award of the International Society of Immunopharmacology 1983
- Award of the Chemical Society of Japan 1999
- Bang Award of the International Society of Endotoxin and Innate Immunity 2004

Nakanishi Symposium 2016

Organized by : Nakanishi Symposium Organizing Committee
Co-organized by: Chemical Society of Japan,
Division of Natural Products Chemistry & Biological Science

Date March 24th, 2016, 13:30-17:30

Venue Doshisha University
(3F 301, Keido-kan Bldg., Kyotanabe Campus)

Program

■ 13:30-14:00 Award Ceremony of Nakanishi Prize 2016

Presider Prof. Michio Murata (Osaka University)

Prize Winner of the Nakanishi Prize 2016:

Dr. Shoichi Kusumoto; Professor Emeritus of Osaka University

■ 14:00-17:00 Nakanishi Symposium

Presider Prof. Minoru Ueda (Tohoku University)

14:00- “*Microbial Immunomodulatory Glycoconjugates; Syntheses and Biological Functions*”

Prof. Yukari Fujimoto: (Keio University)

14:30- “*Nucleic Acid Sensing by Toll-like Receptors*”

Prof. Kensuke Miyake (The University of Tokyo)

Presider Prof. Keisuke Suzuki (Tokyo Institute of Technology)

15:00- “*Identification of a Novel Glycolipid Essential for Membrane Protein Integration*”

Dr. Keiko Shimamoto (Suntory Foundation for Life Sciences)

15:30- “*Quest for Synthetic Chemistry’s Initiative in Glycobiology*”

Prof. Yukishige Ito (RIKEN)

16:00-16:10 ---Break---

Presider Prof. Michio Murata; Osaka University

16:10- **Award Lecture** “*Chemistry and Biological Functions of Bacterial Cell Surface Glycoconjugates*”

Dr. Shoichi Kusumoto

■ 17:10- Closing Remarks

Microbial Immunomodulatory Glycoconjugates; Syntheses and Biological Functions

Yukari Fujimoto

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Microbial surface glyco- and lipid-conjugates often show immunomodulatory activities, and some of these compounds are recognized by the innate immune receptors, such as TLRs, NLRs, RLRs and CLRs, to trigger the immune system. The representative ligands include bacterial lipopolysaccharide (LPS)/lipid A, peptidoglycan (PGN), and lipo peptides.

PGN is a component of bacterial cell wall consisting of long glycans having alternating GlcNAc- β (1 \rightarrow 4)-MurNAc and peptide chains that link the glycans. PGN is recognized by the innate immune receptor proteins, Nod1 and Nod2, in cytosol. We have established the synthesis and then made the compound library of PGN fragments, which would currently be the one of the most comprehensive library in the world. Based on the fragment library, we have analyzed the structure-biology relationships of PGN in the recognition by Nod1 and Nod2, and also found natural Nod1 ligands in the environment.¹ We have also recently revealed that *Mycobacterium* PGN fragments exhibited very weak hNod1 and hNod2 activation, which provide a potential mechanism for *M. tuberculosis* cytosolic immune evasion.²

References:

1. Fujimoto, Y.; Pradipta, A. R.; Inohara, N.; Fukase, K. *Nat. Prod. Rep.* **2012**, *29*, 568.
2. Wang, Q.; Matsuo, Y.; Pradipta, A. R.; Inohara, N.; Fujimoto, Y.; Fukase, K. *Org. Biomol. Chem.*, **2016**, *14*, 1013.

Nucleic Acid Sensing by Toll-like Receptors

Kensuke Miyake

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The Toll family of receptors has critical roles in microbial recognition and activation of defense responses. Nucleic acid (NA) is a major Toll-like receptor (TLR) ligand. TLR3, 7/8, and 9 reside in intracellular organelle and sense double strand (ds) RNA, single strand (ss) RNA, and ssDNA, respectively. A variety of vaccines have been developed by modifying NAs. It is important to understand how NAs are sensed by TLRs. Recently reported TLR9 structure shows that TLR9 binds to short ssDNA fragment. dsDNA is therefore needed to be processed into short ssDNA fragments. DNase II is the one and only DNase functioning in lysosomes. We recently show that DNase II has an important role in processing CpG-A, an oligoDNA strongly inducing type I interferon production in plasmacytoid dendritic cells. CpG-A needs to be cleaved by DNase II into a ssDNA fragment to stimulate TLR9. To develop novel DNA vaccines, it is important to consider how DNAs are metabolized before stimulating TLR9. Small chemical ligands for TLR7 and TLR8 are already used to stimulate immune responses in humans. The structure of TLR8 reveals that a small chemical ligand binds to dimerization interface of TLR8. Another structure of TLR8 with ssRNA shows that TLR8 binds to uridine and di-ribonucleotide UG instead of ssRNA fragment. TLR8 shows higher responses to Uridine and ssRNA than ssRNA alone. TLR8 interaction with Uridine is enhanced in the presence of ssRNA. TLR8 is likely to sense Uridine and oligoribonucleotides. Functional studies further show that TLR7 responds to Guanosine and ssRNA. These results indicate that TLR7 and TLR8 respond to a ribonucleoside with oligoribonucleotide. Further study on the role of ribonucleosides in TLR7/8 responses would contribute to development of novel vaccines.

Identification of a Novel Glycolipid Essential for Membrane Protein Integration

Keiko Shimamoto

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Protein integration into membranes is a major biological event in cells. The process of integration of membrane proteins into biological membranes is basically conserved in all organisms. In *Escherichia coli*, protein integration depends on a translocon that is termed as the SecYEG/SRP (signal recognition particle) system (Figure 1A). In addition, the Sec/SRP-independent pathway is known for a subset of membrane proteins. Recently, Nishiyama et al. suggested the presence of an unknown factor, which is indispensable in both Sec/SRP-dependent and -independent processes, and named it MPIase (membrane protein integrase) after its function.¹

We attempted to identify the factor and elucidate its mode of action.² After many trial and error processes, repeated partition chromatography yielded highly pure MPIase. When the purified MPIase was added into liposomes, in which spontaneous integration was inhibited, a substrate protein (3L-Pf3 coat) was dose-dependently integrated into the liposomes. Moreover, stoichiometric analysis indicated that the number of integrated substrate was higher than that of MPIase; *i.e.*, MPIase catalytically drove 3L-Pf3 coat integration reactions.

Despite its enzyme-like activity, amino acid analysis indicated that MPIase is non-proteinaceous and comprises unstable aminosugars. GC-MS analysis after the methanolysis demonstrated the presence of DAG containing typical of *E. coli* fatty acids. NMR studies of the purified MPIase supported that it is a glycolipid. A pyrophosphate linker between the reducing terminal of the glycan and lipid moiety was demonstrated on ³¹P-NMR of MPIase.

The breakthrough for the structure determination of glycan was MALDI-TOF-MS measurements. A characteristic series of peaks suggested that MPIase contained repeating units. MS/MS analyses indicated that the unit contained three components corresponding to partially *O*-acetylated *N*-acetyl-aminodeoxyhexose, *N*-acetyl-aminohexose, and *N*-acetyl-aminohexuronic acid. Removal of lipid and *O*-acetyl moieties by mild hydrolysis of MPIase gave a simpler MS spectrum, suggesting that MPIase is a mixture of homologous molecules with 9-11 repeating units in the glycan part.

Methanolysis of the glycan gave three major peaks on GC-MS, one of which proved to be glucosamine (GlcNAc). We assumed the presence of 4-acetamido-4-deoxyfucose (Fuc4NAc) from the ROESY spectrum and synthesized authentic Fuc4NAc, which was identical to another peak. Comparison of the remaining peak in GC-MS spectrum with some synthesized authentic uronic acids identified it as 2-acetamido-2-deoxymannuronic acid (ManNAcA). The sequence and linkage mode of the trisaccharide were determined by 2D-NMR and confirmed by synthesis of trisaccharide unit.

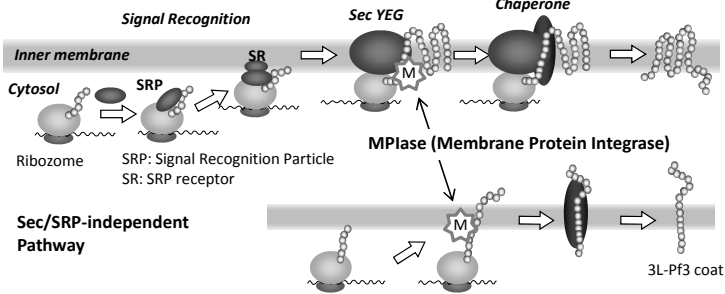
Taking the aforementioned information into account, we determined the structure of MPIase to be as shown in Figure 1B.

Direct interaction between the acetyl groups of glycan of MPIase and 3L-Pf3 coat protein was confirmed in saturation transfer difference-NMR. Although studies to elucidate the mechanisms of MPIase are now in progress, we speculated that its glycan captures substrate proteins to maintain an integration-competent structure (Figure 1C).

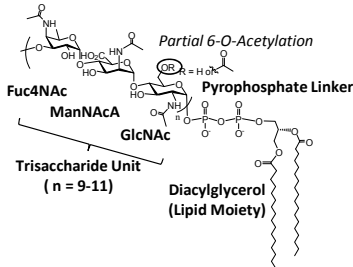
Although MPIase is a glycolipid devoid of a proteinaceous moiety, MPIase exhibited integration-dedicated chaperone-like activity that drove subsequent membrane integration. On the basis of these results, the term “glycolipozyme” was coined to express the enzyme-like activity of MPIase.

A. Membrane Protein Integration Pathways in *E. coli*

Translocon (SecYEG/SRP)-dependent Pathway



B. Structure of Mplase



C. Plausible Working Model

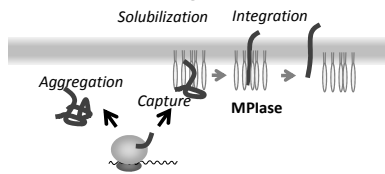


Figure 1. A) Membrane protein pathway in *E. coli*. B) Structure of Mplase. C) Plausible working model of Mplase in 3L-Pf3 integration.

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1. K. Nishiyama, M. Maeda, M. Abe, T. Kanamori, K. Shimamoto, S. Kusumoto, T. Ueda, and H. Tokuda, *Biochem. Biophys. Res. Commun.*, 394, 733 (2010).
2. K. Nishiyama, M. Maeda, K. Yanagisawa, R. Nagase, H. Komura, T. Iwashita, T. Yamagaki, S. Kusumoto, H. Tokuda, and K. Shimamoto, *Nat. Commun.*, 3, 1260 (2012).

Quest for Synthetic Chemistry's Initiative in Glycobiology

Yukishige Ito

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The fields of “Glycobiology” and “Glycotechnology” are gaining an increasing amount of attention. Glycoconjugates, such as glycoproteins, glycolipids, proteoglycans, and microbial cell-surface components, consist of glycan chains. A major part of our research has been directed at the synthesis and functional analysis of glycoconjugate oligosaccharides of various origins.

Biological functions of glycoconjugate glycan chains are numerous. Most typically, these molecules exist at the cell surface and play numerous roles in cellular communication events, such as cell migration, cell-matrix and cell-cell attachment, signal transduction, microbial transfection, cancer metastasis, cell differentiation, and immune responses. They also play fundamental roles in the stabilization of glycoproteins, modulating the 3-D structure and inter- and intracellular transport of proteins.

In order to gain a precise understanding of the functions of glycan chains, access to structurally defined oligosaccharides is required. Eukaryotic cells contain a huge number of glycoproteins. Furthermore, structures of glycoprotein glycan chains are highly diverse. In many cases, glycoproteins consist of various glycoforms, which differ in the number, composition, branching, or terminal modification of glycan chains. Therefore, the isolation of a homogeneous glycoprotein with a defined structure is an extremely difficult task, unless the target protein is exceptionally abundant.

Structures of glycoproteins are characterized by their complexity and diversity. To clarify their functions, synthetic approaches are considered to be promising. Development of synthetic methodologies

useful for efficient and facile preparation of oligosaccharides is a focal issue in carbohydrate chemistry. In light of their structural diversity, practical strategy to facilitate the synthesis of oligosaccharide is expected to be highly valuable. Glycoprotein glycans are known to play numerous biological roles, both intra- and intra-cellularly, through their interaction with various proteins such as lectins, glycosidases, and glycosyltransferases. However, their precise analysis has been hindered by structural heterogeneity of glycoproteins.

Given these circumstances, our effort has been directed to synthesis of glycoprotein glycans and related probes for analysis of their intracellular functions. This talk will cover selected topics among our recent studies on 1) development of novel methods for selective formation of glycosidic linkages,¹⁻³ 2) target-oriented as well as library oriented synthesis of glycoprotein glycans,⁴ 3) analysis of glycan-protein interactions in the ER using synthetic substrates,⁵⁻¹¹ and 4) mechanistic studies on carbohydrate binding agents.¹²

References:

1. A. Ishiwata, et al., *JACS*, 133, 19524 (2011); *JACS*, 133, 2275 (2011)
2. A. Ishiwata, et al., *OBC*, 8, 3596 (2010); *ACIE*, 53, 9812 (2014)
3. H. Satoh, et al., *JACS*, 133, 5610 (2011); S. Manabe et al., *CEJ*, 20, 124 (2014)
4. A. Koizumi, et al., *ACIE*, 52 7426 (2013); K. Fujikawa et al., *CEJ*, 21, 3224 (2015)
5. Y. Ito, et al., *Sem. Dev. Cell. Biol.*, 41, 90 (2015)
6. K. Totani, et al., *Biochemistry*, 48, 2933 (2009)
7. Y. Takeda et al., *Glycobiology*, 24, 344 (2014)
8. K. Ohara et al., *Biochemistry*, 54, 4909 (2015)
9. M. Sakono, et al., *BBRC*, 426, 504 (2012)
10. M. Hachisu et al., *ChemBioChem*, doi.org/10.1002/cbic.201500595
11. M. Izumi et al., *JACS*, 134, 7238 (2012)
12. Y. Nakagawa, et al., *ACIE*, 50 6084 (2011); *JACS*, 133, 17485 (2011); *CEJ*, 19, 10516 (2013)

Chemistry and Biological Functions of Bacterial Cell Surface Glycoconjugates

Shoichi Kusumoto

Professor Emeritus, Osaka University

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Since the middle of the 20th century, certain bacterial cell components were known to nonspecifically enhance the immunological responses of higher animals. These were early observations of a new defense system of animals, which is now well known as innate immunity. Our research group fortunately found opportunities to join this research area and succeeded in identification of the active chemical entities of the immune stimulatory functions of both bacterial cell wall peptidoglycan (PGN) and bacterial endotoxin.

In 1942 Freund et al. first described that heat-killed *Mycobacterium* cells enhanced production of antibody against given protein antigens. Several research groups then proved that PGN ubiquitously distributed on both gram-positive and -negative bacterial cells is responsible for this function. Kotani and his group found that oligosaccharide peptide fractions obtained by controlled enzymatic digestion of PGN showed definite activity to enhance the immunological responses of experimental animals in a way similar to that by intact bacterial cells. In order to identify the active entity, several synthetic *N*-acetylmuramyl peptides from our laboratory were tested by Kotani's group. Among them, *N*-acetylmuramyl-L-alanyl-D-isoglutamine (abbreviated muramyl dipeptide, MDP) was found to exhibit definite activity and thus proved to be the smallest active structure of PGN. It was a quite impressive fact at that time that a small molecular species like MDP represents the function of the entire complex bacterial high molecular component PGN.

During the above study on PGN, we came to know another, more potent bacterial cell surface constituent, “endotoxin”, which was first described by Pfeiffer in 1892 as a potent toxic component of *Vibrio cholera* cells. Westphal and Lüderitz then disclosed that chemical entity of endotoxin is lipopolysaccharide (LPS) which is a common constituent of all gram-negative bacteria. They also described in 1954 that the lipophilic part of LPS, which they named “lipid A”, is the endotoxic active principle.

In spite of intensive investigations by Lüderitz and his successors, the complete and precise chemical structure of lipid A was not elucidated until we succeeded in isolation of a single homogeneous molecular species of a lipid A derivative in 1984. Our chemical and spectroscopic analyses of the purified derivative led to the precise structure of lipid A as an *N,O*-polyacylated glucosamine disaccharide bisphosphate. This conclusion was immediately confirmed by our total chemical synthesis of the proposed structure in 1984: the synthetic lipid A exhibited identical, full biological activities with those of bacterial endotoxin. This was the final unequivocal proof of the concept that lipid A is the active entity of bacterial endotoxin after hundred years of time since its discovery.

After that, precise studies had become possible of the action mechanism of lipid A by the use of synthetic homogeneous preparation and various structural analogues. It was also shown that excessive activation of immune competent cells resulted in serious damage of animals such as high fever, tissue and organ damages, organ failure, or even death of host animals, which was recognized as toxic effects of endotoxin. Around the end of the 20th century, a group of specific receptors named Toll-like receptors (TLRs) was discovered on animal cell membrane. Among them TLR4 was proved to be the specific receptor for endotoxin. The Nobel Prize in Physiology or Medicine in 2011 went to Bruce A. Beutler for his contribution with this regard.

The elaborate defense system of higher animals against invading pathogens was hence disclosed around this period: animals are well prepared by born by having, for example TLR4 which specifically

recognizes endotoxin/lipid A as a signal of invading gram-negative microbes and switches further immunological defense system on to prevent further invasion. In the meantime, another protein Nod2 was discovered and was proved to be a specific receptor for MDP. This means MDP, as another common bacterial cell constituent, also acts as a trigger of the innate immune system.

Thinking back the time when we started our research in this line, nothing was known at all on the innate immune system. We were just simply but strongly interested in the fact that certain bacteria cell surface components, which are normally never present in our own body, activate our defense system: we anticipated the presence of any unknown general defense mechanism. We were thus quite lucky in the point that we came into this expanding but old research field of immunology just on a right moment and were able to contribute to the new development of the research from a side of organic chemists. We very much appreciate the many researchers worldwide for their enjoyable and fruitful interdisciplinary collaborations for over three decades. Now that the research reached to a stage where molecular biological techniques show their strong power, I myself feel that the role of organic chemists in this field became unfortunately less important than before.

References:

1. Key structures of bacterial peptidoglycan and lipopolysaccharide triggering the innate immune system of higher animals: Chemical synthesis and functional studies. S. Kusumoto, K. Fukase, T. Shiba, *Proc. Japan Acad. Ser. B* **2010**, *86* (4), 322-337.
2. Synthesis of endotoxic principle of bacterial lipopolysaccharide and its recognition by the innate immune systems of hosts. S. Kusumoto, K. Fukase, *Chem. Rec.*, **2006**, *6*, 333-343.
3. Synthetic and natural *Escherichia coli* free lipid A express identical endotoxic activities. C. Galanos, O. Lüderitz, E. Th. Rietschel, O. Westphal, H. Brade, L. Brade, M. Freudenberg, U. Schade, M. Imoto, H. Yoshimura, S. Kusumoto, and T. Shiba, *Eur. J. Biochem.*, **1985**, *148*, 1-5.

Yukari Fujimoto: born in 1967 and graduated (B. 1989), and received Ph. D. (2002) from Osaka University (Prof. Shoichi Kusumoto). After industrial experience at Sumitomo Chemical Co., Ltd., post-graduate studies at Columbia University (1998-2001, Prof. Koji Nakanishi), and postdoctoral studies at Nagoya University (2002, Prof. Yoshihito Watanabe), she joined the faculty of Osaka University, as Assistant Professor (2003-2006) (Profs. Shoichi Kusumoto, and Koichi Fukase), then Lecturer (2006-2008), and Associate Professor (2008-2014). Moved to Keio University as a Professor (2014-). Several awards including Incentive Award in Synthetic Organic Chemistry from the Society for Synthetic Organic Chemistry and the Alois Nowotny Award from International Endotoxin & Innate Immunity Society.



Kensuke Miyake is a professor of the Division of Innate Immunity, Department of Microbiology and Immunology, The Institute of Medical Science, The University of Tokyo. He graduated from Okayama University Medical School in 1984, and obtained Ph.D. at Osaka University Medical School in 1988. He joined the laboratory of Dr. Paul W. Kincade as a postdoctoral fellow in Oklahoma Medical Research foundation from 1988-1990. He then returned to Japan and joined the laboratory of Dr. Masao Kimoto in the Department of Immunology, Saga Medical School in 1990. He moved to the University of Tokyo in 2001, and has been in the current position.



Keiko Shimamoto born in Kobe, 1962 and graduated from 1984 Osaka University, 1991, Osaka University, Prof. Shoichi Kusumoto.

Keiko Shimamoto studied organic synthesis at Osaka University under the direction of Prof. Tetsuo Shiba and received her M.S. degree in 1986. She joined Suntory Institute for Bioorganic Research (SUNBOR) in 1986 and is working there as an executive researcher. She received her Ph.D. from Osaka University in 1991 under the supervision of Prof. Shoichi Kusumoto. Her research interests include the investigation of the functions of bioactive amino acids and glycolipids based on the synthesis of novel molecular probes. She was awarded the Yamazaki–Teiichi Prize in 2006 and the Chemical Society of Japan Award for Creative Work for 2013.



Yukishige Ito: born in 1954 and graduated from The University of Tokyo (B. 1977) PhD, The University of Tokyo (Prof. Masaji Ohno) 1982, Postdoctoral fellow, Massachusetts Institute of Technology (1982-1984, Prof. Satoru Masamune), Research Scientist (1984-1996), RIKEN, Senior Scientist (1996-1998), Chief Scientist (1998-), Synthetic Cellular Chemistry Laboratory, RIKEN, Visiting Scholar, Cytel Corporation and the Scripps Research Institute (1991-1993), Research Director, JST ERATO Glycotriology Project (2009-2015). Received awards include Whistler International Award in Carbohydrate Chemistry, Japan Society for Bioscience, Biotechnology, and Agrochemistry Award.



The Recipients of the Prize hereto are:

1996 Yoshimasa Hirata*	2007 Hung-wen Liu
1997 Frank H. Westheimer	2008 Michel Rohmer*
1998 Albert J. Eschenmoser*	2009 JoAnne Stubbe
1999 Jeremy R. Knowles	2010 Shosuke Yamamura*
2000 Satoshi Ōmura*	2011 C. Dale Poulter
2001 John D. Roberts	2012 Daisuke Uemura*
2002 Sir Jack Baldwin*	2013 Arthur G. Palmer, III
2003 A. Ian Scott	2014 Jerrold Meinwald*
2004 Isao Kitagawa*	2015 Fred McLafferty
2005 Stephen J. Benkovic	2016 Shoichi Kusumoto*
2006 Takeshi Yasumoto*	

*Selection and presentation made by the Chemical Society of Japan.

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