Peptides, proteins, and their derivatives have attracted growing interest from both academics and the pharmaceutical industry over the past decades, creating a renaissance in the field of peptide/protein therapeutics. This resurgence not only benefits from but also indeed has stimulated the rapid development of new protein chemistry to access and study these biomolecules. Thus, we are honored to serve as guest editors of this Special Issue of The Journal of Organic Chemistry on Modern Peptide and Protein Chemistry, which includes a variety of cutting-edge contributions from leading experts in the field. This high-quality work will help readers to experience the extensive and in-depth exploration of peptide and protein chemistry and synthesis with an emphasis on the most current progress and functional applications.

**MILESTONES IN PEPTIDE/PROTEIN CHEMISTRY**

The synthesis of peptides and proteins has been gradually advanced during the past century along with the prosperous development of organic chemistry. Several milestone accomplishments originate from the first description and synthesis of a peptide bond in the glycyl-glycine dipeptide by Emil Fischer, who is considered the founder of peptide synthesis. Max Bergmann, one of Fischer’s students, and his doctoral student Leonidas Zervas, introduced the carbobenzyo (Cbz, organic synthesis. Early peptide syntheses were performed in solution and were successfully applied for the first assembly of a polypeptide hormone, oxytocin, by Vincent du Vigneaud, who was awarded the Nobel Prize in Chemistry in 1955.

A leap in practical preparation of more complex peptides was the advent of solid-phase peptide synthesis (SPPS) strategies, pioneered by Bruce Merrifield, who also received a Nobel Prize in Chemistry, in 1984, for “his development of methodology for chemical synthesis on a solid matrix”. The refinement of SPPS strategies has enabled the routine and efficient synthesis of numerous peptides, small proteins, and their synthetic analogues. The subsequent development of chemoselective ligation, in particular native chemical ligation (NCL) by Stephen Kent in 1994 has opened the field of proteins to organic synthesis by facilitating the assembly of multiple unprotected peptide fragments, obtained from SPPS. These reactions, together with the development of semisynthetic strategies, have pushed the size limitation of synthetic proteins to a few hundreds of amino acids.

Besides the approaches to synthesize native peptides and proteins, various synthetic methodologies for accessing derivatives with diversified structures have also been developed, enabling a host of high-precision hypotheses about structure–function relationships to be explored. These include backbone and side-chain modifications, in which the latter can be introduced by bioorthogonal modification reactions, including for example cycloaddition or Staudinger reactions. Importantly, the site-specific introduction of posttranslational modifications into peptides and proteins has been critical for the understanding of their essential role in biological processes. These developments have laid a solid foundation for the current renaissance of peptide and protein therapeutics and simultaneously pushed basic biological and chemical research to new heights.

**CURRENT PROGRESSES IN THIS SPECIAL ISSUE**

This Special Issue of The Journal of Organic Chemistry on Modern Peptide and Protein Chemistry contains 48 research articles from 16 countries. These research articles cover various aspects of modern synthesis and modification of peptides and proteins.

For example, novel peptide ligation methods are featured in this issue. Aspartic acid forming α-ketoacid–hydroxylamine (KAHA) ligations were realized by using (S)-4,4-difluoro-5-oxoproline. Diselenide-selenoester ligation (DSL) was successfully expanded to phenylalanine and leucine at the ligation site via utility of β-selenophenylalanine and β-selenoleucine, followed by application in constructing a glycopeptide and protein UL22A. The utilization of N-terminal Cys/Sec-containing peptides for NCL was facilitated by discovering copper-mediated deprotection of thiazolidine and selenazoline derivatives. Chemical synthesis of functional proteins, such as homogeneous granulocyte-macrophage colony-stimulating factor and human chemokine CXCL14 containing methionine sulfoxide, were achieved by using Se- auxiliary-mediated or S-mediated NCL. Alternative chemoselective reactions, such as metal-mediated Suzuki–Miyaura cross-coupling and azide-ynamido cycloaddition are refined and applied to peptides. Finally, enzyme-mediated peptide synthesis using an immobilized peptide ligase is demonstrated.

Furthermore, new synthetic approaches to construct native peptides and peptide mimetics were described in many contributions to this issue. For example, epimerization-free preparation of C-terminal Cys peptide acid by Fmoc SPPS was realized by using pseudoproline-type protecting group. A new
two-photon cleavable thiol protection group, based on a methoxy-substituted nitrodibenzofuran structure, was developed for SPPS. Along those lines, synthetic schemes for peptide and amino acid mimetics are reported here, such as thioamide peptides, indolizidinone dipeptide mimetics and β2-homologous amino acids.

Another challenge in the field is the requirement to improve the stability, cell permeability, and pharmacologic potency of peptides and proteins. Site-specific modification of these biomolecules by additional chemical moieties provides a general and efficient solution. For example, lipidation at the N-terminus of peptides increases the cytotoxicity of lipovelutibols. PEGylation near a patch of nonpolar surface residues increases the conformational stability of the WW domain. A trimethylammonium cation modification at the C-terminus of Vancomycin improves the pharmacological properties of this antimicrobial agent. A few nonproteinogenic residues, like dehydroamino acids, chiral alkenyl cyclopropane amino acids and aza-glycine, were incorporated within peptides. Meanwhile, late-stage modification provides a simple way to prepare site-specifically modified polypeptides, for instance, by developing sulfonium triggered thiol–yne reaction for cysteine modification, or by using sophisticated disulfide-bond formation reaction and cyanobenzothiazole-mediated cysteine dual labeling. In addition, conformationally strained cyclic peptides are the focus of several publications due to their great potential in therapeutic development. Different peptide cyclization strategies, for example, by using NCL followed copper-mediated deprotection of selenazolidine and employing optimized ring closing metathesis reaction with desallyl side products suppressed, are also reported.

A few publications in this Special Issue are relevant to construct biologically active peptide/protein derivatives for interfering with biomolecule recognition, reflecting the advantages of their specificity and efficacy at their targets. For example, a MUC1 glycopeptide library for positional scanning was constructed and applied to reveal the importance of PDTR epitope glycosylation for lectin binding. A peptide-based multiepitopic vaccine platform was built via click reactions. A cell-permeable cyclic peptidyl inhibitor is presented that modulates the Keap1-Nrf2 interaction.

At last, we would like to highlight an important publication, which concerns the safety of researchers working in the field of peptide synthesis. This study reports the anaphylaxis induced by peptide coupling agents including HATU, HBTU, and HCTU and reminds everyone to employ proper protection against potential health hazard of these reagents.

**OUTLOOK**

Highly efficient synthetic methodologies to access peptides and proteins and their derivatives with diversified structures have accelerated their translational biomedical research and development. Although a wealth of exciting advances in various aspects of peptide and protein chemistry have been reported in this Special Issue and elsewhere, many unsolved problems remain, and complicated challenges still need to be met. We are expecting even more innovative contributions to this field, which can benefit from multidisciplinary thinking and technology that is evolving at high speed. For example, it is still demanding to push the size and complexity of synthetic proteins to greater heights with the help of new chemical strategies and even enzyme-catalyzed reactions. Developments in biosynthesis will help to realize the construction of some unique peptide structures inside the biological systems. Data-mining and machine-learning technologies might facilitate the structural design as well as the synthetic planning of bioactive proteins and their derivatives. As the guest editors of this Special Issue to celebrate the progression of Modern Peptide and Protein Chemistry, we are looking forward to witnessing and participating in the inevitably prosperous future of this field.

![Figure 1](image-url)
FASEB, and cochaired the 22nd American Peptide Symposium and the GRC on Biology and Chemistry of Peptides. He has published over 180 papers and has been honored with an Alfred P. Sloan Foundation fellowship, the Vincent du Vigneaud Award, the Max Bergmann Kreis Gold Medal, the Zervas Award and the RSC MedImmune Protein and Peptide Science Award. Professor Dawson is a pioneer of chemoselective ligation methods for macromolecule synthesis and modification and has applied these tools broadly to better understand biological systems.

Yong-Xiang Chen graduated from Hunan University with a B.S. degree in 2002. She then received a Ph.D. degree under the guidance of Prof. Yan-Mei Li from Tsinghua University in 2007 after which she had worked in the group of Prof. Herbert Waldmann at Max-Planck Institution of Molecular Physiology in Dortmund as an Alexander von Humboldt postdoctoral fellow. Since 2011, she has joined Tsinghua University as an associate professor in the Department of Chemistry. Her current research interests include synthesis of peptides and proteins with posttranslational modifications; application of them in elucidating or interfering the molecular processes of related biological events.

Hironobu Hojo obtained his Ph.D. in organic chemistry from Osaka University in 1994 under the guidance of Prof. Saburo Aimoto on the development of the chemical method for protein synthesis. He then moved to the Osaka City University as lecturer and worked on the development of novel biomaterials. In 1998, he moved to Tokai University as an associate professor. There, he started to develop a facile method for glycoprotein synthesis by collaboration with Prof. Yoshiaki Nakahara. He was promoted to professor of Tokai University in 2007. He moved to the present position, Professor of the Institute for Protein Research, Osaka University, in 2013 and is developing a chemical approach toward the understanding of protein and glycoprotein function.

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