Current Topics

Drug Discovery: Recent Progress and the Future

Foreword

Akira Otaka

Institute of Biomedical Sciences and Graduate School of Pharmaceutical Sciences, Tokushima University; Tokushima 770–8505, Japan.

The Pharmaceutical Society of Japan (PSJ) organizes the International Symposium for Medicinal Sciences (ISMS) series, with pharmaceutical company researchers encouraged to participate in the annual meetings of the PSJ and to create close relationships with international researchers interested in medicinal sciences. The first and second ISMS were held in conjunction with the 135th and 136th annual meetings of the PSJ in Kobe and Yokohama, respectively. The third ISMS, including two invited lectures by Professor Dr. Ross D. King, University of Manchester, U.K., and Dr. Sriram Subramaniam, National Cancer Institute, National Institutes of Health, U.S. and 44 invited poster presentations, was organized during the 137th annual meeting held in Sendai in 2017. Professor King gave a presentation on robot scientists for automating drug design, and Dr. Subramaniam introduced recent advances in cryo-electron microscopy for drug discovery. The contributions from invited poster presenters at the third ISMS included a wide range of topics.

For the Current Topics section in this issue of the Chemical and Pharmaceutical Bulletin, we have assembled four reviews, three communications, and two regular articles that cover the entire drug discovery field including medicinal chemistry, pharmacology, pharmacokinetics, and regulatory sciences.

The first review, entitled Dengue Virus and Its Inhibitors: A Brief Review is by Dr. Yu-Shi Tian and his colleagues. They give an overview of the viral life cycle and present the history of the dengue virus. Their review concludes with a summary of the most recently reported antiviral candidates and promising newly discovered targets.

Supramolecular Pharmaceutical Sciences: A Novel Concept Combining Pharmaceutical Sciences and Supramolecular Chemistry with a Focus on Cyclodextrin-Based Supramolecules was contributed by the group of Dr. Taishi Higashi. The review proposes a new concept termed “supramolecular pharmaceutical sciences,” which combines pharmaceutical sciences and supramolecular chemistry. This concept could be useful for developing new ideas, methods, hypotheses, strategies, materials, and mechanisms in pharmaceutical sciences.

Dr. Masayuki Kuroda and co-workers, in the review entitled A Novel Approach to the Treatment of Plasma Protein Deficiency: Ex Vivo-Manipulated Adipocytes for Sustained Secretion of Therapeutic Proteins, focus on recent progress in gene therapy-mediated enzyme replacement and introduce a different approach using adipocytes to enable lifelong treatment for patients with intractable plasma protein deficiencies.

The fourth review, Establishment of a Patient-Derived Xenograft Model and Application for Precision Cancer Medicine by Dr. Seiji Okada’s research group deals with patient-derived xenograft (PDX) models that can be created with the transplantation of cancerous cells or tissues from patients’ primary tumors into immunodeficient mice. PDXs are now in the spotlight as more accurate human cancer models compared with mice tumor and human cancer cell lines transplanted into mice. PDX technology is expected to lead to breakthroughs with the introduction of novel, highly immunodeficient mice.

Boron-Catalyzed Carboxylic Acid-Selective Aldol Reaction with Trifluoromethyl Ketones, the first communication by Dr. Kouhei Ishizawa, Prof. Motomu Kanai, and their group, focuses on the development of a catalytic carboxylic acid-selective aldol reaction with trifluoromethyl ketones. The newly developed reaction proceeded chemoselectively at the α-position of carboxylic acid even in the presence of ketone, ester, or amide functional groups in the donor substrates. Its chemoselectivity will be beneficial for late-stage derivatizations of biologically relevant compounds.

The second communication, entitled Discovery of a Novel Fluoroquinolone Antibiotic Candidate WFQ-228 with Potent Antimicrobial Activity and the Potential to Overcome Major Drug Resistance, reports on research carried out by Wakanaga Pharmaceutical Company. It explains the development of the novel fluoroquinolone antibiotic candidate WFQ-228, which was shown to exert more potent activity than levofloxacin (LVX) and ciprofloxacin (CIP) against clinical isolates of Pseudomonas aeruginosa, Escherichia coli, and Actinobacter baumannii including quinolone-resistant strains. Furthermore, WFQ-228 demonstrated the potential to overcome major mechanisms of drug resistance, since its antimicrobial activity was less affected by both pump-mediated efflux and mutations of the quinolone resistance-determining region in P. aeruginosa compared with LVX and CIP.

Dihydroorotate Dehydrogenase as a Target for the Development of Novel Helicobacter pylori-Specific Antimicrobials, the final communication written by Dr. Tomokazu Ohishi and co-workers, summarizes the literature on strategies for developing novel therapeutic agents that target dihydroorotate dehydrogenase (DHODH) of H. pylori. The emergence of resistant strains and occurrence of adverse effects as a result of current therapies have complicated the successful eradication of H. pylori infection. Although various antibiotics that target several bacterial enzymes have been discovered, DHODH may hold potential for the development of novel anti-H. pylori agents with reduced toxicity and side effects.

The first regular article, Discovery of 2-[(E)-2-(7-Fluoro-3-methylquinoxalin-2-yl)vinyl]-6-pyrrolidin-1-yl-N-(tetrahydro-2H-pyran-4-yl)pyrimidin-4-amine Hydrochloride as a Highly Selective PDE10A Inhibitor, describes the work...
undertaken by Mitsubishi Tanabe Pharma to develop a phosphodiesterase (PDE) 10A inhibitor, which is expected to become a therapeutic option for the treatment of patients with psychoses such as schizophrenia. The newly developed compound demonstrated effectiveness in the rat conditioned avoidance response test due to strong PDE10A inhibitory activity and favorable pharmacokinetics.

Astellas Pharma contributed the second regular article, Discovery of \( N\)-[2-Methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]-\( N\)'-[2-(propane-2-sulfonyl)phenyl]1,3,5-triazine-2,4-diamine (ASP3026), a Potent and Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor. A series of 1,3,5-triazine derivatives as potent, selective ALK inhibitors was synthesized and evaluated. In mice xenografted with NCI-H2228 cells expressing EML4-ALK, once-daily oral administration of compound ASP3026 demonstrated dose-dependent antitumor activity.

I believe that these reviews, communications, and articles provide useful information that will contribute to advances in medicinal sciences and sincerely thank all authors for their significant contributions.