Peptides 2008 Award Recipients

Anna Maria Papini introduced the "Chemical Reverse Approach" to develop post-translational modified peptides as synthetic probes to detect and fishing out specific and high affinity antibodies as biomarkers of autoimmune diseases. As a proof of concept she developed a glycopeptide-based immunoassay, MS PepKit, diagnostic/prognostic test for Multiple Sclerosis. Professor Papini´s main research interests are in the field of chemistry and physics of biomolecules for life sciences studying peptides and proteins involved in the molecular mechanisms of physiological and pathological conditions. She is involved in the development of synthetic & semi-synthetic strategies to co- or post-translational modified peptides, in particular glycoconjugates as diagnostic and prognostic tools for human, animal, and plant diseases. Characterisation of biomarkers of disease activity, with a particular attention to "theranostics", achieved through immunochemistry studies, using conventional assays and innovative techniques for example for biosensors or electrochemical devices. Her strong commitment in synthesis of biomolecules has been focused to the development of efficient strategies to exotic amino acids orthogonally protected for peptide synthesis (constrained amino acids, glycosyl and lipophilic amino acids), cyclic peptide and peptidomimetic analogues (dicarba analogs, clicked peptides), coupling reagents for solid phase chemistry (amide and ester bond formation) by conventional and alternative approaches (microwave-assisted synthesis). In 2003 she founded the first Academic Spin-off of the University of Florence, EspiKem Srl, Contract Research Organization involved in isolation, characterisation, design, and synthesis of post-translational modified peptide, peptidomimetic, and protein antigens for in vitro diagnostics. Since 2007 she is CSO of the start-up company Toscana Biomarkers Srl that she founded as an R&D Biotech for innovative diagnostic/prognostic assays based on post-translational modified peptides.

Horst Kessler studied chemistry in Leipzig and Tübingen, where he received his Ph.D. degree with Eugen Müller in 1966. Shortly after his habilitation in 1969 he was appointed full professor for organic chemistry at the J. W. Goethe University in Frankfurt in 1971. In 1989 he moved to the Technische Universität München. He is also head of the Bavarian NMR Center. Guest professorships lead him to Halifax, Tokyo, Madison, Haifa, Austin, and Jerusalem. In October 2008 he will become Carl von Linde Professor (Emeritus of excellence) at the Institute of Advanced Studies of the TUM. The main achievements of Professor Dr. Horst Kessler which went into the practice include design, synthesis and preclinical development of Cilengitide, a drug currently in clinical phase III for treatment of glioblastoma (developed by Merck KGaA, Darmstadt), efficient implant coating of Titanium implants for stimulated osseointegration (approved by Biomet Germany, Berlin) and cancer imaging via "Galacto-RGD" for PET based molecular imaging (used in the Klinikum rechts der Isar in München and now worldwide to detect metastasis). His interests in the area of bioorganic and medicinal chemistry are wide on the study of biological recognition phenomena and on conformationally oriented design of biologically active molecules, including peptides, peptidomimetics, carbohydrates and nucleic acid. Chemical synthesis of peptides, sugars and their mimetics, aim to conversion of peptides and small molecules into orally available drugs. Professor Kessler´s candidate drug screening technology is in advanced application of nuclear magnetic resonance (NMR). Professor Kessler develops and applies new NMR techniques to determine structure and dynamics of biomolecules, especially of proteins and their complexes with ligands of low and high molecular weights. Biomaterials used on implant surface for stimulation of cell-adhesion and specific labeling of integrin ligands for tumor diagnostics and therapy belong in the repertoire in use of his molecules in biomedicine. Horst Kessler is holder of about 625 publications, 35 patents, and has provided over 600, mostly invited and often plenary lectures in the field, his editorial board contributions throughout his carrier is in over 20 journals. Professor Dr. Kessler is the recipient of the Otto Bayer award (1986), the Max Bergmann medal for peptide chemistry (1988), the Emil Fischer medal (1997), the Max-Planck-Forschungspreis (2001), the Vincent Du Vigneaud Award of the American Peptide Society (2002), the Hans Herloff Inhoffen Medal (2002) and the Burkhart Helferich Award (2005). In 2002 he received the honorary degree of the University of Leipzig. He is a member of the "Bayerische Akademie der Wissenschaft" and the "Deutsche Akademie der Naturforscher Leopoldina".

Manfred Mutter made substantial contributions to the field of Peptide Chemistry over more than 30 years. In particular, his originality and scientific intuition have resulted in the establishment of a number of fundamental concepts, which belong to today's standard tools in peptide research and which have served as a platform for numerous extensions and applications in synthetic and biomimetic chemistry. Out of more than 300 original publications, reviews and book contributions, the following contributions may be highlighted: Conformational aspects in peptide synthesis: MM has been pioneer in delineating the importance of conformational changes during chain elongation and their impact on physical properties. PEG-peptides for studying conformational transitions: PEG-bound peptides ('Liquid-Phase -Synthesis') allowed the conformational study of otherwise insoluble peptides for the first time (partially in collaboration with Claudio Toniolo). Template-assembled synthetic proteins (TASP) in protein de novo design: The template concept found broad application in diverse fields of peptide and protein chemistry (see chapter in Houben-Weyl). Pseudo-Prolines in peptide synthesis and biomimetic chemistry: The introduction of Pseudo-prolines as solubilising, structure disruptive protection technique has become a widely used tool in the synthesis of hydrophobic peptides. In addition, the tailored induction of cis-bonds into peptide backbones has opened versatile applications in biochemistry (see book chapter in C. Dugave, 'Cis-trans Isomerization in Biochemistry', 2006). Switch-Peptides as folding precursors in self-assembling peptides: The recently developed concept of 'switch-peptides' for studying the molecular origin of amyloid beta based conformational transitions (see review in Biopolymers/ Peptide Science, 2006) has found a broad echo in the 'amyloid-community' for its potential in biochemical/biophysical studies of degenerative diseases. Beside his innovative contributions in peptide chemistry, Manfred Mutter is well known as an inspiring and motivating speaker, making him one of our outstanding representatives at international conferences. Last but not least, being in the process of retirement, the dedication of this prestigious award represents a well-earned distinction for an outstanding scientist and a personality with a fine sense of humour. Professor Dr. Manfred Mutter is presently affiliated with Debiopharm S.A., CH- 1002 Lausanne, Switzerland. E-mail: mmutter@debiopharm.ch

Miklos Bodanszky session

MB01

Introduction

Martinez, Jean
Max Mousseron Biomolecule Institute (IBMM), CNRS, Montpellier, FRANCE

MB02

VIP almost 40 years later: Diverse functions and therapeutic promise

Said, Sami I.
State University of New York, Stony Brook, Departments of Medicine, Physiology & Graduate Progr. Pharmacology, UNITED STATES

Soon after Viktor Mutt and I, in 1970, reported its isolation from porcine duodenal extracts, Miklos Bodanszky successfully synthesized the Vasoactive Intestinal Peptide (VIP), and characterized its chemical nature. Intensive research by numerous investigators over the years since has revealed VIP to have multiple biological effects, important physiological influence in many organ systems, and strong promise as a therapeutic agent for a number of varied human disorders. Produced mainly in neurons of the central and peripheral nervous systems, VIP is therefore widely distributed throughout the body. Its biological actions include: Relaxation of vascular and non-vascular smooth muscle, inhibition of smooth muscle cell proliferation, suppression of inflammation, modulation of immune function, and anti-apoptotic, pro-survival effects. Among its likely physiological roles, deduced in part from studies of mice lacking the VIP gene and the use of specific antibodies, VIP serves as: A co-transmitter, with NO and CO, of non-adrenergic, non-cholinergic smooth muscle relaxation; a modulator of inflammation, apoptosis, and smooth muscle cell proliferation; and a promoter of cell survival.

Based on the preceding information, as well as on the use of the peptide in experimental models of disease, and in some instances on early clinical trials, VIP and its analogs may prove to be novel and effective agents for the treatment of a variety of human disorders. These include: Bronchial asthma; pulmonary hypertension; Acute Lung Injury/Acute Respiratory Distress Syndrome (ARDS); Multi-Organ Dysfunction Syndrome (MODS); inflammatory/auto-immune disorders, such as rheumatoid arthritis and inflammatory bowel disease; cardiovascular disorders; neurodegenerative diseases, including Alzheimer's disease; and small-cell lung cancer.

After some delay, the pace of progress in this area seems to be accelerating. There is thus reason to hope that the promise fueled by much work, inspired and supported by Viktor Mutt and Miklos Bodanszky, will soon be fulfilled.

MB03

Potent and selective peptide agonists for human melanocortin receptors 1b and 5

Bednarek, Maria A
Merck Research Laboratories, UNITED STATES

α-Melanocyte-stimulating hormones (αMSH), through interactions with the cell surface receptors (melanocortin receptors 1, 3, 4 and 5; MC1,3-5R), elicits numerous physiological functions in the CNS and periphery. Of those receptors, MC1R and MC5R have been predominantly found on the surface of several types of skin and immune cells, in a number of endocrine and exocrine glands, and others. To elucidate and differentiate the role of MC1R and MC5R in some skin disorders, and immunomodulatory and anti-inflammatory actions of αMSH, selective ligands for are necessary.

In the structure of the endogenous agonist - αMSH, the His^{6}-Phe^{7}-Arg^{8}-Trp^{9} segment has been recognized as critical to molecular recognition at hMC5R and hMC1bR (an isoform of the human MC1aR with virtually identical pharmacological properties). The same segment has also been crucial for potency of various synthetic analogs of αMSH at hMC1b,5R. One of the most broadly used analogs of αMSH is a cyclic peptide, Ac-Nle^{4}-cyclo-(Asp^{5}-His^{6}-D-Phe^{7}-Arg^{8}-Trp^{9}-Lys^{10})-NH_2, designated MTII. Herein, the role of Trp^{9} in the interactions of MTII with the hMC1b,5R was examined through the ligand structure -function studies. The side chain of Trp^{9} was found to be not critical for high agonist potency at the hMC1b,5R; however, it was essential for potency of the MTII peptides at the human melanocortin receptors 3 and 4 (hMC3,4R). Several analogs of MTII are reported which are potent agonists at hMC1bR or hMC5R, and of high receptor subtype selectivity.

MB04

Peptides Containing Novel Tyrosine Analogues: Pharmacological Tools, Systemically Active Opioid Analgesics and Cell-Penetrating, Mitochondria-Targeted Antioxidants

Schiller, Peter W.
Clinical Research Institute of Montreal, CANADA

Syntheses of novel analogues of 2',6'-dimethyltyrosine (Dmt) lacking the amino group and, in some cases, containing a -$CONH_2$ function in place of the phenolic hydroxyl group or various substituents at the β-carbon were developed. Substitution of these analogues for Tyr^{1} in opioid peptides resulted in highly selective δ- or κ-opioid antagonists, the first opioid peptide-derived high affinity μ opioid antagonist and a mixed κ agonist/μ antagonist. The dermorphin-derived tetrapeptide H-Dmt-D-Arg-Phe-Lys-NH_2 ([Dmt^{1}]DALDA) is a highly selective μ opioid agonist showing subnanomolar potency in vitro, stability against enzymatic degradation and a long elimination half-life, capable of producing a potent, centrally mediated analgesic effect when given i.th. or s.c. Conjugates of [Dmt^{1}]DALDA linked to a δ opioid antagonist