SYNTHETIC LIPOPEPTIDES: A VIABLE APPROACH FOR THE THERAPEUTIC VACCINES OF THE FUTURE?

H.S. Gras-Masse

Faculty of Biological and Pharmaceutical Sciences, Lille, France

Therapeutic vaccination against infectious diseases is an attractive complement to conventional drug therapy of viral or parasite infections. Current literature reveals the growing interest for extremely reductionist approaches aiming at producing totally synthetic vaccines that would be fully defined at the molecular level and particularly safe. Analysts and medicinal chemists have joined forces with immunologists and taken up the clear challenge of identifying immunologically active structural elements and synthesizing them in pure, reproducible forms. With the goal of producing an improved vaccine that should ideally induce a multispecific response in non-selected populations, we have elected to focus our efforts upon the design end synthesis of cocktail-lipopeptides vaccines for inducing helper T cell (HTL) as well as cytotoxic T lymphocytes (CTL) responses. The interest of cocktail-lipopeptide vaccines has now been confirmed by several phase I and phase II clinical trials The stimulation of professional antigen-presenting cells represents another promising approach for the improvement of vaccine efficacy. In this context, the mannose-receptor represents an attractive entry point for the targeting and activation of dendritic cells with antigens linked to clustered glycosides or glycomimetics. The ability of single-chain lipopeptides to gain access to cellular compartments other than those related to degradation/recycling is illustrated by the Interferon-gamma receptor agonist activity a lipopeptide containing the sequence responsible for the recognition of the cytoplasmic domain of the receptor. Such compounds could find utility for the polarisation of the immune response towards a TH1 profile.

DISULFIDES IN PEPTIDES AND PROTEINS A PERSONAL CHALLENGE FROM PAST TO PRESENT

L. Moroder

Max-Planck-Institut Fur Biochemie, Martinsried, Germany

With oxytocin/vasopressin as monocystine peptide hormones followed by insulin as a double-stranded disulfide-crooslinked peptide molecule as ambitious targets, the synthesis of multiple-cystine containing peptides has been a challenge since the pioneering days of peptide chemistry. For decades this has fostered the development of orthogonal thiol-protection schemes and of efficient chemistries for regioselective disulfide formation. With the increasing knowledge of oxidative refolding mechanisms of multiple-cysteine peptides and proteins and by sampling experiences with natural bioactive peptides in their post-translational mature forms as well as with protein subdomains, Anfinsen´s principle of the sequence-encoded structural information for correct refolding processes was repeatedly confirmed with success. In fact, an increasing number of cystine-crossbridged peptides from different sources and active as toxins, inhibitors and other regulatory molecules retain sufficient inherent information for correct oxidative refolding into their native structures, although generally processed from folded precusors. These unidirectional processes can be ameliorated by opportune manipulation of experimental conditions or by induction of productive intermediates, e.g. exploiting the redox potential of the isosteric selenocysteine. But generally the robustness of the natural folds is such that deliberate changes in the cystine connectivities can only be achieved either by regioselective disulfide chemistry or again applying the selenocysteine approach. Insightful conclusions could be drawn from small protein subdomains, e.g. the IgG hinge domain, and short natural peptides as the toxin apamin and the heads of nematocysts minicollagen about the thermodynamically coupled process of folding and disulfide formation. However, there are also cases where folding has to preceed disulfide formation as in the case of the collagens´ cystine knots which still make the synthetic approach indispensable for installing the desired cystine connectivities.

MURRAY GOODMAN, TEACHER, MENTOR, FRIEND

F. Naider

Department of Chemistry, College of Staten Island, CUNY, Staten Island, New York NY, USA

Professor Murray Goodman, an internationally renowned peptide chemist, passed away in Germany on June 1, 2004 at the age of 75. Dr. Goodman earned his doctorate in the laboratory of the Nobel Laureate, Melvin Calvin and began his career at the Polytechnic Institute of Brooklyn in 1956, after postdoctoral studies at MIT and Cambridge University. In 1970 Murray moved to the University of California, San Diego as Professor of Chemistry. He was author of nearly 500 journal articles, Editor-in-Chief of the recently published 5 volume compendium entitled Synthesis of Peptides and Peptidomimetics, and founding Editor of Biopolymers and the Journal of Peptide Science. Professor Goodman was an inspiring teacher of organic and polymer chemistry and mentored 85 doctoral students and more than 200 postdocs, many of whom became leaders in peptide chemistry in countries throughout the world. He received numerous prizes including The Ralph Hirschmann Prize in Peptide Chemistry , The Herman F. Mark Polymer Chemistry Award and the Pierce (Merrifield) Prize sponsored by the American Peptide Society. The breadth of Murray's research and his ability to contribute to diverse areas of peptide science were the hallmarks of his career. He examined synthetic and biologically active peptides and conducted a broad array of biophysical analyses. He was a leader in peptide synthesis and protein secondary structure, in racemization and coupling chemistry, in peptidomimetics and peptide sweeteners. Murray Goodman was a passionate man who recognized the great potential for peptide science. He tirelessly advocated for the next generation of peptide chemists who were pushing forward the frontiers of our field. Murray will be remembered as an international ambassador for peptide chemistry. He was a frequent attendee at European Peptide Symposia beginning in the 1960s. Scientists from nearly every country were frequent guests at his home. They all considered him to be their friend and came to him for advice. Murray was highly supportive of his students and followed their careers long after they left his group. His group reunions at peptide symposia were truly international events that grew in size from year to year. The outpouring of condolences upon his untimely passing testify to the revered place he held in our discipline. He was a teacher, a mentor and a friend to all of us. He will be greatly missed