# 8. Uluslararası Farmasötik Teknoloji Sempozyumu (IPTS-96)'nun ardından...

## "Protein Drug Delivery and Vaccine Development"

The advent of synthetic peptides and recombinant proteins revealed the need for viable alternatives for the presently used injectable dosage forms and for the exploration of alternative drug and vaccine delivery routes. At the 8th International Pharmaceutical Technology Symposium entitled "Recent Advances in Peptide and Protein Delivery" the delivery problems and potential solutions were addressed by 27 experts in the field. The symposium organised by Hacettepe University Faculty of Pharmacy from September 9-11 offered in its programme an excellent review of the present status and also new insights in potential future developments.

After a general introduction in the field of protein drug delivery by Prof. Robinson (Univ. of Wisconsin), Prof. Hashida (Kyoto Univ.) showed by means of clearance diagrams how the pharmacokinetic properties of a protein can be directed by chemical modification to optimise its therapeutic efficacy. Alternative drug delivery routes discussed were the peroral route (Prof. Junginger), the nasal route (Dr. Hussain), the buccal route (Prof. Squier), and the enteral route (Prof. Nagai). Prof. Torchilin discussed lymphatic delivery. It was demonstrated that poly(acrylate) derivatives are not only able to deactivate the local enzymes in the GI-tract, but also can improve intestinal membrane permeability. Stabilisation of nasally administered pentapeptide against nasal aminopeptidases was achieved in case the N-terminal aminoacid was an acidic aminoacid. An advantage of the use of the buccal route for protein drug delivery is the absence of proteolytic enzymes. The buccal tissue may retain drug in the intercellular spaces of its epithelial layers that may serve as a kind of drug reservoir to release compounds into the oral cavity by a "back-diffusion" process.

Dr. Kate demonstrated in-vitro the potential in-vivo carrier capability of multivesicular liposomes (Depofoam) for the sustained subcutaneous or intravenous application of proteins such as IGF-1 and IL-2. The intratumour delivery of tumour-specific cytotoxic monoclonal anti-nucleosome auto-antibodies from aged animals was shown by Prof. Torchilin to result in strong tumouricidal action in different types of tumours: this exciting finding may open up the door to fundamentally new ways of combating cancer.

Developing stable formulations for biopharmaceuticals in anything but straightforward. Due to their proteineous nature all biotech products presently on the market and under clinical investigation are administered parenterally in a liquid formulation or a lyophilised form which has to be reconstituted prior to application. Dr. Wallach (Boehringer Ingelheim) reviewed how biopharmaceutical formulations for tissue plasminogen activator, interferon, and monoclonal antibodies were obtained with adequate stability.

A substantial part of the presentations was devoted to immunology and vaccine development. Dr. Allison (DAWA Corporation) gave a fine introduction, whereas Prof. Alpar (Aston Univ.) addressed the new opportunities for the delivery of vaccine antigens via mucosal and parenteral routes by biodegradable microspheres. Poly(L-lactic acid) microspheres prepared by a double emulsion technique with polyvinylpyrrolidone in the primary emulsion rendered the highest antibody response for BSA, but not for tetanus toxoid, indicating that these vaccine formulations have to be optimised on an individual basis. Development of a peptide vaccine for immunocontraception (Prof. Goldberg) resulted in a synthetic peptide epitope of the sperm-specific isozyme of lactate dehydrogenase with a significant immune response in rabbits and female baboons. The 37-aminoacid long peptide contains both the B-cell epitope and a so-called "promoscuous" T-cell epitope, effective in a broad range of the population. Prof. Mustefaev (TÜBİTAK Marmara Research Centre, Gebze) discussed a novel immunogenic system based on temperature - responsive polymer conjugates with proteins. Polymer/protein conjugates

are also widely used in the area of drug targeting, as was reviewed by Prof. Özer (Hacettepe Univ.). To avoid covalent modification of the targeted molecule, bifunctional antibodies may be used. The plasma proteinase inhibitor alpha-2 macroglobulin was suggested as a novel agent for antigen delivery to macrophages to enhance antibody formation.

The symposium was closed with a Round Table discussion focusing on the regulatory aspects of protein medicines and vaccines. Mr. Fairchild of the EMEA (European Medicines Evaluation Agency) emphasized the important role of quality assurance at all stages of a medicines' life cycle: from as early as the conception and development phases to as late as the distribution and product surveillance phases. Detailed information on the EMEA can be obtained from Internet free of charge. Dr. Spieser from the Biological Standardisation Division of the European Pharmacopoeial Commission demonstrated the importance of well characterisation of synthetic biologicals and of standardisation in the regulatory specifications for the different hepatitis B vaccines, insulins, erytropoietins and somatotropins on the market. Aside from the production of specific product monographs, the European Pharmacopoeia Commission is also involved in the standardisation of general texts and methods, e.g. for cell cultures, tests for mycoplasm, sterility, endotoxins and for PCR-methodology. More details of the work of the Division can be found in a special journal issue on Biologicals of European Pharmacopoeia Forum Dr. Sam (N.V. Organon) exemplified the regulatory requirements for protein products by describing chemistry and pharmacy aspects for recombinant Follicle Stimulating Hormone (Puregon), a glycoprotein for which recently an EU marketing authorisation was obtained. His presentation was concluded with a short introduction of the concept of the "Well-Characterised Product" (WCP) as a new category for biotechnology derived drugs. The WCP status would probably result in more characterisation and validation work in the development stage, but once licensed would allow for much less routine testing and elimination of individual lot release as required by the FDA for biotech medicines. At present there are no official guidelines and regulations for the measurement of the toxicity of adjuvants for vaccines. Prof. Stewart-Tull described the current toxicity testing for adjuvants and immunomodulators to be used in human vaccines. He warned for a short-sighted ban of adjuvants based on old data, since some of these studies have been performed with adjuvants of ill-defined quality. Adjuvant researchers should seek for a compromise, leading to adjuvant molecules that stimulate immunopotentiation and at the same time have reduced tissue reactivity.

In total 58 posters were presented on a wide spectrum of pharmaceutical topics including pharmacognosy, pharmaceutical technology and drug delivery. The IPTS-96 Poster Award was won by S. Uslu, A. Yüksel and Prof. Baykara, all from Ankara University. The title of the poster was "Investigation of the effects of urea, DMSO and oleic acid on release from methyl salicylate from topical preparations added lyotropic liquid crystals". All oral contributions will be published as full papers in the Minutes series of Editions de Santé. This book will be available in the first quarter of 1997. I am looking forward to IPTS-98.

**Dr. Tom SAM**

*Düzeltme :*

Geçen sayımızda, aşağıda isimleri yazılı makalelerin geliş ve kabul tarihlerinin yazılması unutulmuştur. Düzeltir, özür dileriz.

- Analysis of Syrups Containing Chlorpheniramine Maleate, Codeine Phosphate and Ephedrine Hydrochloride by Derivative UV Spectrophotometry
  G.T : 6.10.1995
  K.T : 11.6.1996

- Epidermal Büyüme Faktörü(EGF)'nün Yara İyileşmesindeki Rolü
  G.T : 24.7.1995
  K.T : 4.3.1996

- *Peganum Harmala* L. Bitkisi ve Biyolojik Aktif Bileşikleri
  G.T : 13.3.1995
  K.T : 5.3.1996