

## GUEST EDITORIAL

PSEUDOALLERGY AND OTHER IRREGULAR  
IMMUNE RESPONSES TO DRUG CARRIERS

During the last few years, experimental and clinical studies have indicated anomalous immune responses to a range of drug carrier systems. Such phenomena have included dose- and treatment-schedule-dependent changes in the pharmacokinetics of long-circulating nanoparticles and liposomes, and acute allergic reactions to some clinical formulations of liposomes and micelles that occur without sensitization. This special issue of *Critical Reviews in Therapeutic Drug Carrier Systems* focuses on understanding the principles behind these irregular immune reactions. The subject of the reviews is unique in that it represents a multidisciplinary approach comprising clinical medicine, material sciences, immunology, pharmacology, toxicology, polymer and colloid chemistry, and lipid biochemistry to unravel the principal mechanisms in this challenging area.

The articles in this volume consider three intriguing concepts, which are of considerable theoretical and practical importance in medicine. The first is addressed by Moghimi and Hunter in their article, "Capture of Stealth Nanoparticles by the Body's Defenses." They have principally identified the fundamental importance of the state of responsiveness of macrophage subpopulations, as well as humoral immune responses to polymeric coating materials, to the recognition and clearance of long-circulating nanospheres from the vasculature. Laverman et al., in their article, "*In Vivo* Applications of PEG-Liposomes: Unexpected Observations," discuss the importance of short-term humoral immune responses to long-circulating liposomes, which results in their rapid recognition and clearance from the blood by macrophages of the reticuloendothelial system. This phenomenon thus resembles the induction of specific humoral and cellular immune responses by classical antigens in an atypical manner.

A novel concept is discussed in the final review in this series, "Complement Activation: Related Pseudoallergy Caused by Liposomes, Micellar Carriers of Intravenous Drugs, and Radiocontrast Agents." This article suggests that complement activation plays a causal role in a large number of previously poorly understood pseudoallergic reactions to a number of intravenously administered liposomal and micellar products (e.g., Doxil® and Taxol®). Reactions engendered by such formulations can be severe—even fatal—and may represent a significant logistic and financial burden on hospitals. The review also proposes an update of Gell and Coombs' classification of allergy types to incorporate "complement activation-related pseudoallergy" (CARPA) as a novel subcategory of Type I hypersensitivity reactions.

It is therefore of fundamental importance that irregular immune responses to drug carriers are understood to ensure their future rational design and evaluation. For example, there is no known clinical or laboratory test at present that can predict pseudoallergic reactions to advanced formulations among individual subjects. The above-mentioned drugs are widely used despite their reactogenicity, probably because in cancer chemotherapy, their indication area, there is more tolerance for side effects.

By providing a comprehensive and thorough analysis of the above irregular immune responses to drug-carrier systems, the present articles will increase our awareness of these phenomena and inspire new concepts for the further development of this field. I would like to express my appreciation and gratitude to the Editor-In-Chief, Dr. Stephen Bruck, for recognizing the novelty and importance of this subject and for giving me the opportunity to be a guest editor for this topical issue.

*Janos Szebeni, M.D., Ph.D.*

*We will miss him ...*

THE TRAGIC passing away of Dr. Stephen Bruck is a great loss for his family, the publisher and readership of this journal, as well as for the scientific community as a whole. Personally, I am mourning a distinguished mentor and supporter, a dear senior friend. Our common professional interests and his Austro-Hungarian roots, feeding a keen interest in Hungarians and their affairs, earned me unique opportunities to spend time and learn about him. Much could be told about the life of this man of extraordinarily broad knowledge and intense curiosity, underlying his devotion to and precision in editing this journal. Nevertheless, what I admired most in him was his youthful spirit and optimism in engaging in a variety of endeavors that would challenge the energy of people half of his chronological age. This openness and enthusiasm for science and many other arts of life make his premature death all the more tragic. He will remain in my memory as an ever-young man of boundless horizon, as I knew him.

*J.S.*