The focus of DMPK Theme Issues is state of the art and recent developments in research areas that have significant relevance for the academic world as well as for the pharmaceutical industry. The three issues that have appeared to date deal with drug-metabolizing enzymes, membrane transporters and pharmacokinetics and pharmacodynamics. This issue is dedicated to a water-soluble protein transporter, namely human serum albumin (HSA), and presents strategies for utilizing its unique ligand binding capability, and the latest news concerning its metabolism. This information can be useful in terms of the development of new compounds – drugs, albumins or albumin-ligand complexes – that can be used diagnostically or therapeutically.

A considerable proportion of compounds with other biological activity fails to progress to later stages of drug development due to problems associated with absorption, distribution, metabolism and elimination (ADME). Because ADME is a complex issue, the cost of development of new drugs is increased considerably. This factor constitutes one of the main driving forces in the search for techniques to improve ADME characteristics in the early stages of drug development. The ligand binding properties of HSA and its abundance in the body couples the protein closely to the ADME problem. Therefore, detailed information regarding binding sites and ligand-induced conformational changes of HSA are critical to solving this problem. Recent X-ray crystallography and site-directed mutagenesis studies have contributed significant, new information in this area. Such information can be used to determine whether a new drug in spe should be constructed in such a way that it makes use of, or avoids, albumin transport and depot function. Molecular information is also very useful in related contexts, because it provides basic information on how to modify a protein or ligand for producing complexes with new properties. For example, modified albumin-heme complexes have the ability to reversibly bind to molecular oxygen; the aim of this research has been to construct an artificial hemoprotein. Furthermore, a complex of HSA and carboxy-C60-fullerene may become a useful photosensitizer for photodynamic therapy of cancer.

In addition to the reversible binding of ligands, HSA binds to xenobiotics and endogenous compounds in a covalent manner and thereby effects the metabolic fate and clearance of certain drugs. However, complex formation may produce a protein with new functions and possible clinical applications. Thus, HSA can be S-nitrosylated by nitric oxide, and the resulting compound may have antibacterial and cytoprotective properties. The production of fusion proteins involves a completely different type of covalent binding. Because of its relatively high in vivo half-life of approximately 19 days, HSA is an attractive fusion partner for extending the half-life of peptides and small proteins.

Little information is available concerning interplay between reversibly bound ligands and covalent binding of other compounds. However, this interplay may be valuable when designing or improving new albumin functions. For example, the reversible binding of endogenous fatty acids appears to improve the cytoprotective effect of S-nitrosylated HSA by facilitating S-transnitrosation from HSA to cellular target proteins.

The binding of a drug to albumin has significant effect on the pharmacokinetics and pharmacodynamics of many drugs, but such binding can also be clinically very relevant outside the body. Extracorporeal albumin dialysis serves to illustrate this point. By this technique, it is possible to remove albumin binding toxins and drugs from the body. The method will probably be improved in the future by constructing HSA mutants with increased affinity for the compound that is intended to be removed from a patient’s body.

The in vivo binding properties of HSA can be modified by many factors. If an unambiguous link exists between the provoking factor and the type of modified binding, this can be used diagnostically. Thus, in myocardial ischaemia, the N-terminal part of HSA is modified in such a way that its ability to bind certain metal ions is lost. In practice, binding is monitored by using cobalt ions as a representative ligand.

Clinically, HSA is used for the restoration of blood volume, emergency treatment of shock, acute management of burns and other situations associated with hypoproteinemia. In such situations it would be beneficial to have access to albumins with prolonged lifetime in the circulation. Therefore, much research is currently being conducted on albumin-isofoms, -fragments and -dimers, in attempt to find such a protein. If the protein carries a useful drug or other therapeutical agent, it would improve the clinical situation even further. Modified HSA is used for other in vivo purposes such as targeting individual types of cells or organs. The main purpose of such targeting is to obtain specific delivery of
an albumin-bound drug. For example, lactosylation, mannosylation and succinylation target HSA to hepatocytes, Kupffer cells and endothelial cells of the liver, respectively.

A recent landmark in our understanding of the normal metabolism of HSA is the discovery of its pH-dependent interaction with the intracellular neonatal Fc receptor (FcRn). This receptor prevents a large fraction of albumin and IgG from degradation in lysosomes and sends it back for reuse in the circulation and other extracellular spaces. Interference with the interaction between the protein and receptor would likely modify the half-life of albumin, albumin-bound drugs and albumin fusion proteins in a therapeutically useful way.

Thus, modern albumin research has progressed from the mere determination of binding site number and corresponding association constants to the development and characterization of albumin isoforms and albumin-ligand complexes with new therapeutical or diagnostic functions. Several examples of such possibilities are described and discussed in greater detail, including methodological aspects, in the seven expert reviews in this Theme Issue. The reports were first presented at an international symposium entitled “Development of albumins with new functions and clinical applications” held on October 30, 2008 in Kumamoto, Japan. We hope that these reviews will stimulate more work and the development of new ideas in this promising and growing field of research. Finally, we wish to sincerely thank all the contributors and readers of this fourth Theme Issue of DMPK.

Masaki Otagiri
Graduate School of Pharmaceutical Sciences, Kumamoto University

Ulrich Kragh-Hansen
Department of Medical Biochemistry, University of Aarhus

Teruko Imai
Graduate School of Pharmaceutical Sciences, Kumamoto University