PROTECTIVE EFFECT OF S-NITROSYLATED HUMAN SERUM ALBUMINS TO ORGAN INJURY
Shinji Yoneshige1, Yu Ishima1, Ayaka Suenaga1, Hiroshi Watanabe1,2, Masaki Otagiri1,3, and Toru Maruyama1,2
1Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-hommachi, Kumamoto, 862-0973, Japan, 2Center for Clinical Pharmaceutical Sciences, School of Pharmacy, Kumamoto University, 5-1, Oe-hommachi, Kumamoto, 862-0973, Japan, 3Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto, 860-0082, Japan.

[Purpose] Human serum albumin (HSA) is the most abundant circulating protein and its S-nitrosylated form serves as a reservoir of nitric oxide (NO) produced by endothelial cells. Previously, we found that S-nitrosylated HSA (SNO-HSA) significantly reduced the tissue or cellular damage associated with reperfusion. In this study, we investigated whether SNO-HSA showed the reduction of organ damages harvested from experimental animals during storage because ischemia/reperfusion-associated tissue alterations still represented a major drawback in organ transplantation.

[Methods] We prepared four kinds of SNO-HSAs with the different degrees of S-nitrosylation and mannosylation (Man) (mono-SNO-HSA, poly-SNO-HSA, mono-SNO-Man-HSA and poly-SNO-Man-HSA). The total concentrations of NO metabolite (NOx; nitrite and nitrate) in tissues were measured by HPLC. Organs were harvested from experimental animals following by the standard procedures of organ transplantation.

[Results and Discussion] SNO-HSAs significantly inhibited apoptosis induced by oxidative stress. Intracellular NO levels were increased by the presence of SNO-HSAs. Supplementation of SNO-HSAs improved the viability of harvested organs during preservation. However, the extents of these effects were different between SNO-HSAs.

[Conclusion] These results suggested that the pretreatment of SNO-HSA might have a potential for ex vivo augmentation of organ viability during preservation.

IN-VIVO DISPOSITION CHARACTERISTICS AND ANTI-TUMOR ACTIVITY OF DOXORUBICIN-ENCAPSULATING NIOSOMES
Shuhei Nishiguchi, Tamer Shehata, Tatsuya Miyata, Ken-ichi Ogawara, Toshikiro Kimura and Kazutaka Higaki
Division of Pharmaceutical Sciences, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University 1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan.

[Purpose] Niosomes are defined as non-ionic surfactant (NIS)-based vesicles possessing an aqueous core enclosed by bilayer structure like liposomes. In this study, we prepared various naked and PEGylated niosomes composed of NISs with diverse physicochemical properties, and evaluated in-vivo disposition characteristics of niosomes and anti-tumor activity of niosomes encapsulating doxorubicin (DOX-niosomes).

[Methods] Niosomes were prepared by hydration method. In-vivo disposition characteristics of niosomes after intravenous injection were assessed in normal rats. In-vivo disposition characteristics including the tumor disposition of DOX and in-vivo anti-tumor activity of DOX-niosomes after intravenous injection were evaluated in solid tumor-bearing mice inoculated with Colon-26 carcinoma cells (C26).

[Results and Discussion] Among NISs tested so far, PEGylated niosomes composed of Span 20, Span 40, Span 80 or Brij 72 exhibited dramatically longer blood circulation time than each corresponding naked niosomes. Among them, higher tumor disposition of DOX and significantly higher in-vivo anti-tumor activity were correspondingly confirmed in the case of PEGylated DOX-niosomes composed of Span 20 or Brij 72 than each naked niosomes. Similar evaluations for other niosomes are underway.

[Conclusions] PEGylation of niosomes with adequate composition significantly prolonged their blood circulation time and delivered sufficient amount of DOX into tumor tissue. These pharmacokinetic advantages of DOX-niosomes would have led to potent in-vivo anti-tumor effect of DOX.