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## Development of a New Gut-targeted Oral Typhoid Vaccine Ty21a

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*Salmonella typhi* Ty21a is an attenuated strain of *S. typhimurium* and used for oral typhoid vaccine. In an attempt to increase the stability of Ty21a manufacturing typhoid vaccine, the stability of freeze-dried Ty21a including additives at various temperature conditions was studied. In order to investigate the freeze-drying rate of Ty21a according to various absorbance, Ty21a was lyophilized by using 8% sucrose as a stabilizer. The optimal freeze-drying rate of Ty21a was appeared when OD (optical density) value of the growth was between 2.5 and 3.0. To investigate the stability of Ty21a at various temperature, the viability was measured after storing the freeze-dried Ty21a at the room temperature, cold and freezing condition for 1 week. The viability of Ty21a in cold and freezing storage condition was 5 times more stable than in room temperature. To search the most stable additives for the freeze-dried Ty21a, the viability of Ty21a including additives at the various storage condition was estimated. Mannitol and lactose were the most stable additives. These results suggest that the OD value of Ty21a growth, low temperature, mannitol and lactose are important factors for the optimal freeze-drying rate, the stable storage and the most stable additives, respectively.

To increase the viability of oral typhoid vaccine during the passage through the gastrointestinal tract, numerous attempts have been made including the vaccine coating. However, problems such as high death rate during the coating process and its instability in the gastric juice still remain to be solved. In this study, the oral vaccine was made as the micro-enteric beads by adding *Salmonella typhi* Ty21a cells to sodium alginate solution and spraying onto calcium chloride solution (ionotropic gelation method). The vaccine showed more than 90% of its original viability after treating it for 1 hour in the artificial gastric juice (37°C, 300rpm). The clearance rate of the Ty21a in the liver and spleen of the mice orally administrated with coated Ty21a was similar to that of the mice intraperitoneally administrated with uncoated Ty21a. The

peripheral blood lymphocytes(PBL) isolated from the mice orally administered with the vaccine produced 15.5 fold higher specific IgA antibody titer than that from the control mice administered with saline solution. Furthermore, the mice treated with the coated Ty21a had higher survival rates (50~87%)than the control mice treated with saline solution (0~10%) in the intraperitoneal challenge test with wild type *S. typhi* Ty21a cells. These results suggest that the alginate-based coating technique is effective to protect live Ty21a from acidic environments, and produces better intestinal immune responses there by providing a potentially excellent oral typhoid vaccine.