**Development of rice-based oral vaccine MucoRice-CTB_19A for the proof of mucosal IgA antibody induction in humans and aiming its application for the creation of a novel normal temperature storage type oral vaccine platform against respiratory infections.**

Hiroshi Kiyono／Chiba University

MucoRice-CTB is a rice-based oral vaccine against cholera and traveler's diarrhea. For clinically advancing MucoRice-CTB as a new generation of plant-based oral vaccine, Phase I studies with original MucoRice-CTB 51A were conducted in Japan and U.S., and its safety and tolerability were verified. The studies demonstrated the induction of antigen (Ag)-specific serum antibodies with the toxin neutralizing activity. However, the studies could not demonstrate the induction of Ag-specific secretory IgA (SIgA) which provides direct neutralizing activity in human intestine. Further, originally planned dose escalation study with MucoRice-CTB 51A was unable to conduct due to insufficient large-scale production. To overcome these scientific and practical concerns, our efforts have been aimed at the development of large-scale production adopted MucoRice-CTB 19A for the newly developed LED-based hydroponic harvesting facility with reduced electricity consumption. In this study, we are now positioning of directly demonstrating the induction of gut CT-specific neutralizing SIgA antibodies in humans by using a new scale-upped MucoRice-CTB19A consisting of one copy of the transgene inserted into chromosome 1. A seed bank of MucoRice-CTB19A has been also established for stably producing the rice vaccine carrying the proposed studies. A first aim of the study is to conduct a double-blind, randomized, placebo-controlled, dose-escalation(6g-18g) phase I study in healthy female and male subjects at Chiba University Hospital and demonstrate the induction of Ag-specific CT neutralizing SIgA in human intestinal secretions by orally-administered MucoRice-CTB 19A. The new result generated by the proposed clinical study will lead to build scientific foundation for subsequent Phase II with a cholera challenging study. A second aim of the proposal is advancing MucoRice system to develop new shelf-stable stockpile-type universal oral vaccines against respiratory infectious diseases (influenza virus and RSV). We plan to develop MuocRice-CTB-RSV rice and MucoRice-CTB-Flu rice, against RSV (types A and B) and influenza virus type A using SHe and M2e antigens, respectively using MucoRice-CTB as a mucosal vaccine delivery modality. MucoRice-CTB-SHe and MucoRice-CTB-M2e will be tested their efficacy for the induction of respective virus-specific protective immunity in rodent models of mouse and/or cotton rat. After establishing the proof of concept of MucoRice-CTB-SHe and MucoRice-CTB-M2e, maker-free line of these MucoRice will be developed for the preparation to advancing clinical study. For the preparation of the next

pandemic, our research will be aimed at accelerating the MucoRice production duration by the modification and optimization of vaccine antigen gene insertion and expression system in rice seeds.