antibodies to rotavirus but instead induces heterotypic cross-protective immunity by eliciting strong T helper (Th) cell responses which promote cross-reactive immunity (Burns JW et al., 1996 Science; Parez N et al., 2004, J Virol). VP6-specific CD4+ Th cells provide cognate help to B cells specific for neutralizing epitopes on the VP7 and/or VP4 molecules (Esquirel FR, Arch. Virol 2000, 145, 813). In addition, VP6-specific CD4+ Th cells were shown to protect against murine rotavirus infection either by a direct cytotoxic mechanism in mucosa or by antiviral cytokines production.

Given the severity of rotavirus and norovirus infections and deficiencies in the currently available vaccines, there is a need for both non-live norovirus and rotavirus vaccines, especially for the prevention of acute gastroenteritis in childhood. Immune responses to NV and RV are complex, and the correlates of protection are not completely elucidated. Collectively, the above-described unique properties attributed to the VLPs including NV VLPs and to the VP6 protein of RV suggest that a vaccine consisting of these two components represents a viable strategy to immunize against NV and RV infection.

BRIEF DESCRIPTION ~~OF THE INVENTION~~

The present disclosure~~invention~~ is based on the surprising finding that norovirus and rotavirus antigens comprised in a combination vaccine do not interfere with each other but elicit a synergistic immunity against each of the antigens present in the vaccine.

In one aspect, there is~~The present invention thus~~ provides~~d~~ a vaccine composition comprising at least one norovirus VLP antigen and at least one rotavirus VP6 antigen.

In some embodiments, the vaccine composition further comprises a norovirus antigen selected from a group consisting of antigenic capsid peptides, and antigenic capsid proteins. The antigen may be derived from any norovirus strain, such as those belonging to GI and GII genogroups and any genotypes thereof. In some embodiments, the norovirus antigen is GII-4 VLP, preferably in a monovalent form. In some other embodiments, the norovirus antigen comprises more than one VLP type.

In some embodiments, the rotavirus VP6 antigen is selected from a group consisting of rVP6 protein, double-layered VP2/VP6 VLP and VLPs comprising VP6 protein. The rVP6 may be in the multimeric form of tubules, spheres or sheets.

In one aspect, there is provided the vaccine composition as defined herein for use in preventing a disease selected from a group consisting of norovirus and rotavirus infection, viral-induced diarrheal and vomiting diseases, and gastroenteritis.

The present disclosure~~invention~~ further provides a use of the described vac-

cines for preventing gastroenteritis, especially in young children. This embodimentaspect of the disclosureinvention may also be formulated as a method of preventing gastroenteritis in a subject in need thereof, especially a young child, comprising vaccinating the subject with a vaccine composition described herein.

In one aspect, there is provided a method of producing a vaccine composition as defined herein, comprising co-expressing at least one norovirus VLP and at least one rotavirus VP6 antigen in a single host, or comprising the steps of a) producing, isolating, and purifying at least one norovirus VLP antigen; b) producing, isolating, and purifying at least one rotavirus VP6 antigen; and c) mixing said norovirus and rotavirus antigens.

Furthermore, the present disclosureinvention provides a method of producing vaccine compositions described herein. The method comprises i) co-expressing at least one norovirus and at least one rotavirus antigen in a single host, or ii) the steps of a) producing, isolating, and purifying at least one norovirus antigen; b) producing, isolating, and purifying at least one rotavirus antigen; and c) mixing said norovirus and rotavirus antigens. Preferably, the antigens are produced in a recombinant baculovirus-infected insect cell host.

Other objects, aspects, details, and advantages of the present disclosureinvention will become apparent from the following drawings, detailed description, and examples.

BRIEF DESCRIPTION OF THE FIGURES

In the following, the invention will be described in greater detail by means of preferred embodiments with reference to the attached figures, in which

Figure 1 A is a photograph of a page blue stained 12% SDS-PAGE gel demonstrating the purity of baculovirus expressed norovirus GII-4 VLPs (lane A), rotavirus rVP6 (lane B), double-layer VP2/VP6 VLPs (lane C), cocktail vaccine (norovirus GII VLPs + rVP6; lane D), and chimeric vaccine (co-infected norovirus GII-4 capsid and rotavirus VP6; lane E). Different proteins are indicated by arrowheads to the right of the gel. Corresponding molecular weights (kDa) of the each protein are indicated to the left of the gel.

Figure 1 B shows electron micrographs of the morphological structures assembled by the recombinant proteins. The proteins were purified and the structures were examined by electron microscopy, followed by staining with 3% uranyl acetate. VLP structures were detected for norovirus (NV) GII-4 capsid, and rotavirus (RV) VP2/VP6 (panels A and C) and tubular structures were observed for VP6 protein (panel B). Both GII-4 VLPs and tubules of VP6 were observed in panel D (cocktail vaccine formulation) and panel E (chimeric vaccine formulation).

Figure 2 illustrates the result of an ELISA assay of a norovirus (NV)-specific IgG response after immunizations of BALB/c mice with different doses