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Recent progress in human mucosal vaccine development: Role of mucosal immunity and mucosal microbiome in the outcome of vaccine effectiveness

One of the most successful and enduring accomplishments of mankind to date is the prevention or effective control of many infectious diseases through the use of vaccines. Most vaccines have been administered via the systemic (intramuscular/intracutaneous/subcutaneous) route. Such vaccines have resulted in significant decline in the disease burden of systemic infections associated with blood stream involvement, such as diphtheria, tetanus, pertussis, hemophilus influenzae, mumps, measles, rubella, and in the complete eradication of smallpox, Poliovirus type2 infection, and virtual elimination of other poliovirus types in most parts of the world. Systemic immunization has been highly effective in inducing systemic innate and adaptive immune responses, but limited or variable degree of immunity in the mucosal sites. Most human infections are acquired via the external mucosal surfaces of the respiratory, gastrointestinal, urogenital tracts. Human and other mammalian mucosal surfaces are in continuous contact with external environment and exposed to an overwhelming spectrum of microorganisms, dietary agents and other environmental macromolecules. It is estimated that the human intestinal mucosa alone contains > bacterial organisms representing as many as 2000 species, and over virus -like particles/gm of feces, of nearly 1,000 viral species. In addition to the bacteria and viruses, human mucosal surfaces are the primary portals of entry and sites of initial colonization with many fungi and parasitic agents. However, pathogenic agents represent a very tiny fraction of the entire mucosal microbial repertoire. The mucosal surfaces of the human neonate begin to be colonized with components of maternal microbiome shortly before, during the process of birth and, subsequently within the first 2-3 weeks after birth from maternal and other environmental exposures. Studies over the past 5 decades have demonstrated an extensive and intercommunicative network of innate and adaptive immune mechanisms in the mucosa associated lymphoid tissue(MALT) distributed in the gut (GALT), upper Respiratory and bronchial epithelium (BALT), nose-nasopharynx-waldyers ring(NALT), Sublingual tissue(SLT),Urogenital tissue and mammary glands, and Skin(SALT). These lymphoid elements are collectively referred as the common mucosal Immune system. There is now increasing evidence to suggest that induction of protective immune response in the specific mucosal portals of entry is the most effective approach to regulate local colonization and subsequent disease outcome. Currently available mucosal vaccines include vaccines against, polioviruses,(live attenuated- oral) rotavirus (live attenuated–oral) *influenza virus* (live attenuated–nasal), *vibrio cholera* (inactivated-oral) and *salmonella typhi* (live attenuated-oral). Several other candidate mucosal vaccines are currently undergoing evaluations in human trials. These include, enterotoxigenic *E.coli* (ETEC), *Shigella*, *Helicobacter*, *Campylobacter*, *Salmonella paratyphi*, and *Norovirus*. The composition and the diversity of mucosal microbiome have been shown to have a profound influence on the induction of immune response and efficacy of mucosally introduced vaccines, especially in tropics. Other possible factors which influence the effectiveness of mucosal vaccines include, methods delivery of the infant (vaginal vs C-section), postnatal feeding practices, malnutrition and carbohydrate consumption, use of antibiotics, and mucosal inflammation. Currently, mucosally delivered vaccines comprise of non- replicating whole organisms, synthetic peptides, inactivated toxins, and recombinant subunit proteins. In order to improve their immunogenicity and protective efficacy, the use of adjuvants has been explored in several clinical trials. These include, adjuvants which facilitate effective delivery of vaccine antigens (liposomes, nanogels, oil-in-water emulsions); adjuvants directed at targeting vaccine antigens to professional antigen presenting cells (APC) (Virosomes). Finally, several

adjuvants which stimulate the immune system itself are being explored currently in different settings. These include molecules binding to specific cellular receptors such as TLR, NOD and RIG1 like receptors, and DNA sensors.

Speaker Biography

Dr. Ogra's scientific contributions include ; characterization of Mucosa associated lymphoid tissue, and mucosal Immune responses in natural or vaccine induced infections with poliovirus, rubella, mumps, hepatitis B virus and enteroviruses; maternal-neonatal interactions of human milk and breast feeding; analysis of host-pathogen interactions underlying the pathogenesis of respiratory syncytial virus infection and demonstration of virus specific IgE; pathogenesis of Rotavirus enteritis; and immunologic aspects of Otitis media. He served as the chief of Pediatric infectious diseases and Professor of Pediatrics and Microbiology at State University of New York, and subsequently as the John Sealy Distinguished Chair Professor and Chairman of Pediatrics at the University of Texas Medical Branch. He has been a member of many national and international scientific societies, NIH study sections, advisory panels of WHO, National academy of Sciences, European union and other global health organizations. He has trained over 78 post-doctoral scholars and has contributed over 440 peer reviewed scientific publications, and 20 full-length books and monographs and has served as the founding editor of the first comprehensive textbook of Mucosal Immunology.

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