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**Title: Regulation of humoral responses in cattle**

**Abstract**

Current vaccination protocols for cattle favor the use of multivalent live attenuated or subunit vaccines, which are administered prior to slaughter or introduction of animals to milk production facilities. In many cases, a vaccine may be administered immediately prior to shipping and housing in high density production facilities, such as feedlots for beef cattle. For most vaccine applications in food animal species, the induction of long-term memory responses is not a requirement but instead a rapid and sustained neutralizing or antigen-binding (blocking) antibody response is needed to control the spread of pathogens. Another situation involves control of pathogen spread in the course of an agrobioterrorism event or natural outbreak of highly infectious agents, such as foot and mouth disease (FMDV). Using the established "ring" vaccination strategy in immunologically naive populations for infection, the induction of neutralizing antibody occurs within 1-2 days. Furthermore, this type of strategy is ideal since the initiation of a robust T helper type (T<sub>H</sub>)1 response occurs 6-7 days post infection, which is not ideal in order to control highly infectious pathogens. Therefore, vaccines that elicit potent immune responses that are independent of T cell help would prevent the spread of contagious pathogens and would be ideal for the prevention of response to a potential agrobioterrorism attack. **Our central hypothesis is that antigen delivery and presentation in the appropriate context will allow the development of relatively rapid antigen-specific antibody responses within 24-48 hours post vaccine administration by IgM plasmablasts and by 72 hours IgM- or IgG-secreting plasma cells (PC).** Secretory IgA (SIgA) constitutes the largest component of the humoral immune system of the body with gram quantities of this isotype produced by mammals on a daily basis. Secretory IgA (SIgA) antibodies function both by blocking pathogen/commensal entry at mucosal surfaces and by virus neutralization within endothelial cells. Several pathways of induction of IgA responses have been described which depend on T cells (T cell dependent or TD) pathways or are independent of T cells (T-independent or TI) and are mediated by dendritic cells (DC) and/or epithelial cells. Many elements of IgA regulation readily cross species barriers (adjuvants, soluble and cognate factors) and are highly conserved whereas other pathways may be more specific to any given species and must be evaluated. Regulation of IgA production in cattle is not completely understood and thus we have focused in part on highly conserved factors (as described in mouse and human), including (TNF-superfamily members (A Proliferation-Inducing Ligand, APRIL and BlyS), neuropeptides which interdigitate mucosal tissues (vasoactive intestinal peptide or VIP), and a small peptide (IgA inducing peptide or IGIP) which can serve as targets for modulation and increasing SIgA virus-specific antibodies. We have evaluated the potential utility of modulating these factors *in vitro* in regulation of qualitative aspects of antibodies of the IgM, IgG and IgA isotypes at mucosal surfaces and in secretions of the upper and lower respiratory tract to a virus of economic and public health importance, foot and mouth disease virus (FMDV). IgA responses in cattle are essential for host defense in response to various infectious agents. IgA is not released into the colostrum as is the case for other mammals but not cattle in which IgG1 is selectively transported. IgA has been shown to be regulated in previous studies in cattle by several cytokines including IFN-gamma, Type I interferons such as IFN-alpha and IFN-tau, transforming growth factor beta, IgA inducing peptide and other potential factors which have not yet been fully evaluated in cattle such as APRIL and BlyS. Many of these factors, namely TGF-beta and type I interferons block cell cycle progression which is an essential component of Ig class switching and thus these factors require additional regulatory factors such as IL-2 to drive cells through cell cycle resulting in class switch recombination. Among these factors, IgA inducing peptide was originally identified from a bovine gut associated

lymphoid tissue expression library and is highly conserved in pigs and humans at >90% at the amino acid level. The factor is regulated differently in various species but is consistently produced by dendritic cells.