

BENZONAPHTHYRIDINE COMPOSITIONS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Patent Application Nos. 61/323,725 filed on Apr. 13, 2010 and 61/413,658 filed on Nov. 15, 2010, the entire teachings of which are incorporated herein by reference.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made in part with Government support under Defense Threat Reduction Agency Contract No. HDTRA1-07-9-0001; and 4.10022-08-RD-B and TMTI0039-09-RD-T, and the U.S. Army Medical Research and Materiel Command Grant No. W81XWH-09-0176. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Recently developed attenuated pathogen or subunit protein vaccines, while offering significant advantages over the traditional whole pathogen vaccines in terms of safety and cost of production, generally have limited immunogenicity as compared to whole pathogens. As a result, these vaccines typically require adjuvants with significant immunostimulatory capability to reach their full potential in preventing diseases.

[0004] Efforts have been made to identify new immunomodulators for use as adjuvants for vaccines and immunotherapies. In particular, an adjuvant formulation that elicits potent cell-mediated and humoral immune responses to a wide range of antigens in humans and domestic animals, but lacking the side effects of conventional adjuvants and other immune modulators, would be highly desirable. This need could be met by small molecule immune potentiators (“SMIPs”) because the small molecule platform provides diverse compounds for the selective manipulation of the immune response, necessary for increasing the therapeutic index immune modulators.

[0005] Toll-like receptors (TLRs) are a group of pattern recognition receptors which bind to pathogen-associated molecular patterns (PAMPS) from bacteria, fungi, protozoa and viruses, and act as a first line of defense against invading pathogens. TLRs are essential to induce expression of genes involved in inflammatory responses, and TLRs and the innate immune system are a critical step in the development of antigen-specific acquired immunity.

[0006] Thirteen TLRs (named TLR1 to TLR13) have been identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species. In particular, TLR7 mediates recognition of microbial nucleic acids such as single stranded RNA. TLR7 comprises a subfamily of TLRs which is located in endosomal or lysosomal compartments of immune cells such as dendritic cells and monocytes. Specifically, TLR7 is expressed by plasmacytoid dendritic cells and to a lesser extent by monocytes. Agonists of TLR7 stimulate the production of various inflammatory cytokines including interleukin-6, interleukin-12, tumor necrosis factor-alpha, and interferon-gamma. Such agonists also promote the increased expression of co-stimulatory molecules such as CD40, CD80, and CD86, major histocompatibility complex molecules, and chemokine receptors. The type I interferons, IFN- α and IFN- β , are also produced by cells upon activation with TLR7 agonists.

[0007] Certain benzonaphthyridine compounds that bind to TLRs, including TLR7 and TLR8, have an immunostimulating effect.

[0008] Viral hemorrhagic fevers refer to a group of illnesses that are caused by four distinct families of RNA viruses: arenaviruses, filoviruses, bunyaviruses, and flaviviruses. These four families of viruses cause different types of viral hemorrhagic fever: Lassa (arenavirus), Marburg (filovirus), Ebola (filovirus), Crimean-Congo (bunyavirus).

[0009] Filoviruses are enveloped, non-segmented viruses with a negative-sense, single-stranded RNA genome of approximately 19 kb. Filoviral infections continue to present an unresolved obstacle in the epidemiology of infectious agents. Moreover, their acuteness is associated with consequent economic and social disruption, severely impacting the areas where the outbreak was epidemic. Ebola and Marburg viruses are members of the Filoviridae family of the order Mononegavirales. Ebola and Marburg viruses cause acute, lethal hemorrhagic fevers for which no vaccines or established treatment currently exist. However, antiviral drugs (ribavirin) as well as generally supportive therapy that replenishes intravenous fluids, maintains blood pressure, and other bodily functions are administered to mammals (e.g. human beings) infected with hemorrhagic fevers. Ebola viruses cause hemorrhagic fever with mortality rates up to 88%. Together with Marburg virus, the five species of Ebola virus (Zaire, Sudan, Reston, Ivory Coast, and Bundibugyo) comprise the family Filoviridae. Whereas Marburg, Ebola Zaire and Ebola Sudan viruses are pathogenic in humans, apes, and monkeys, Ebola Reston is pathogenic only in monkeys. Early immunosuppression may contribute to pathogenesis by facilitating viral replication. Lymphocyte depletion, intravascular apoptosis and cytokine dysregulation are prominent in fatal cases.

[0010] A need exists for compositions that can be used to generate, modulate, or potentiate an immune response in a subject exposed to or infected with a hemorrhagic fever virus, such as Marburg virus or Ebola virus.

SUMMARY OF THE INVENTION

[0011] As described and exemplified herein, the inventors have found that compositions comprising benzonaphthyridine SMIPs are effective hemorrhagic fever virus therapies (e.g., Ebola virus therapies).

[0012] The present invention relates to methods for treating a subject who has been exposed to a hemorrhagic fever virus such as a Filoviridae virus (e.g., Ebola virus). The present invention also relates to compositions for the treatment of exposure to a hemorrhagic fever virus such as a Filoviridae virus (e.g., Ebola virus). Additionally, the invention provides methods for inducing or potentiating an immune response to a hemorrhagic fever virus. The invention also provides compositions for inducing or potentiating an immune response to a hemorrhagic fever virus.

[0013] Also provided is an immunogenic or pharmaceutical composition comprising one or more benzonaphthyridine small molecule immune potentiators (SMIPs) that are agonists of Toll-like receptor 7 (TLR7). Also provided is a composition comprising a benzonaphthyridine TLR7 agonist or salt, solvate, or derivative thereof for use as a medicament.

[0014] One aspect of the invention provides a method of potentiating an immune response in a subject who has been exposed to a hemorrhagic fever virus, comprising administering to said subject a pharmaceutically effective amount of