THERAPEUTIC USE OF A TLR AGONIST AND COMBINATION THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[01] This application claims priority to, and the benefit of, U.S. provisional application No. 61/388,953, filed October 1, 2010, U.S. provisional application No. 61/388,967, filed October 1, 2010, and U.S. provisional application No. 61/390,447, filed October 6, 2010~~, the contents of which are incorporated herein by reference in their entireties~~.

FIELD OF THE INVENTION

[02] The present invention is directed to formulations of a TLR agonist, preferably a TLR8 agonist, and a combination therapy comprising administration of a TLR8 agonist and an anti-cancer agent for use in the treatment of cancer.

BACKGROUND OF THE INVENTION

[03] Stimulation of the immune system, which includes stimulation of either or both innate immunity and adaptive immunity, is a complex phenomenon that can result in either protective or adverse physiologic outcomes for the host. In recent years there has been increased interest in the mechanisms underlying innate immunity, which is believed to initiate and support adaptive immunity. This interest has been fueled in part by the recent discovery of a family of highly conserved pattern recognition receptor proteins known as Toll-like receptors (TLRs) believed to be involved in innate immunity as receptors for pathogen associated molecular patterns (PAMPs). Compositions and methods useful for modulating innate immunity are therefore of great interest, as they may affect therapeutic approaches to conditions involving cancer, infectious disease, autoimmunity, inflammation, allergy, asthma, graft rejection, graft versus host disease (GvHD), and immunodeficiency.

[04] Toll-like receptors (TLRs) are a family of type I transmembrane proteins whose in vivo activation initiates an innate immune response involving specific cytokines, chemokines and growth factors. While all TLRs can activate certain intracellular signaling molecules such as nuclear factor kappa beta (NF-kB) and mitogen activated protein kinases (MAP kinases), the specific set of cytokines and chemokines released appears to be unique for each TLR. TLR7, 8,

or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0119] ~~All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference.~~ Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same.

[0120] The invention is further defined by reference to the following examples, which are not meant to limit the scope of the present invention. It will be apparent to those skilled in the art that many modifications, both to the materials and methods, may be practiced without departing from the purpose and interest of the invention.

1.5 Examples

[0121] Example 1: TLR8 Agonist and Doxil chemotherapy potently activate human antitumor immune response in a human immune system mouse model

[0122] Because of differences between mouse and human immune systems, many of the effects of immunomodulatory drugs cannot be fully studied in syngeneic mouse models. A novel tumor-bearing mouse model with human immune system (HIS) was generated to study interactions between chemotherapy and immune modulatory therapy. The individual effects and the interactions between doxorubicin, a drug which induces immunogenic tumor cell death and activates antigen-presenting cells, and VTX-2337, a TLR8 agonist, which induces potent activation and type 1 polarization of human myeloid DCs were tested and showed reduced activity on murine leukocytes. Nod/SCID/ILRγc knock out (NSG) mice were inoculated with human CD34+ cord blood cells from HLA-A2+ human donors; transplanted s.c. with human HLA-A2+ OVCAR5 ovarian cancer tumors; and treated with pegylated liposomal doxorubicin (Doxil or PLD); VTX-2337; or the two agents in combination. NSG-HIS mice exhibited a full human hematopoietic system, including human monocytes, macrophages and plasmacytoid and myeloid DCs as well as T cell subsets. In NSG-HIS mice, VTX-2337 induced dose-dependent activation of human CD14+ and CD11c+ cells in vivo within 6 hrs. Transient, dose-dependent upregulation of human Th1 cytokines but also IL-10 was observed in the plasma of mice treated

[0171] In sum, it was observed that weekly subcutaneous administration of the novel TLR8 agonist VTX-2337 was generally safe and well tolerated; plasma levels of VTX-2337 and PD responses to VTX-2337 increased in a dose dependent manner; and that subcutaneous administration of VTX-2337 stimulated the production of multiple inflammatory mediators including cytokines and chemokines consistent with activation of an innate immune response.

~~INCORPORATION BY REFERENCE~~

~~[0172] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.~~

EQUIVALENTS

[0173] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.