IMO-9200, A NOVEL CLINICAL-Stage TLR ANTAGONIST FOR THE TREATMENT OF AUTOIMMUNE DISEASES, INHIBITS TLR-MEDIATED IMMUNE RESPONSES AND SHOWS ACTIVITY IN ANIMAL MODELS

Lakshmi Bhagat, Daqing Wang, Wayne Jiang | Idera Pharmaceuticals, Inc. Cambridge, MA 02139, U.S.A.

INTRODUCTION

TLR antagonists can modulate the immune responses triggered by various TLR agonists. Endo-LR7 and TLR9 are expressed on plasmacytoid dendritic cells (pDCs) and B cells, and TLR8 is expressed on myeloid dendritic cells. During breakdown of self-tolerance, in autoimmune diseases, these TLRs regulate immune responses involving self-antigens and self-reactive T cells. Characterization of self-tolerance in autoimmune disease, however, TLR antagonists inhibit immune responses involving self-antigens and self-reactive T cells, leading to improved immune responses including inhibition of TLR and other cytokines, thereby exacerbating the disease.

METHODS AND RESULTS

ENDOSOMAL TLRs ARE IMPLICATED IN THE PATHOGENESIS OF MULTIPLE AUTOIMMUNE DISEASES

BACKGROUND AND OBJECTIVES OF CURRENT STUDIES

METHODS AND RESULTS

ENDOSOMAL TLRs ARE IMPLICATED IN THE PATHOGENESIS OF MULTIPLE AUTOIMMUNE DISEASES

The pathway of immune activation mediated by the endosomal TLRs 7, 8, and 9 in autoimmune disease/pathology has not been well characterized.

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

IMMO-9200 INHIBITS TLR7, 8, AND 9 AGONIST-INDUCED NF-κB ACTIVATION IN HUMAN CELLS

The pathway of immune activation mediated by the endosomal TLRs 7, 8, and 9 in autoimmune disease/pathology has not been well characterized.

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

IMMO-9200 INHIBITS TLR7, 8, AND 9-MEDIATED CYTOKINE INDUCTION IN HUMAN PBMCs IN A DOSE-DEPENDENT FASHION

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

IMO-9200 INHIBITS TLR7, 8, AND 9-MEDIATED B CELL PROLIFERATION IN A DOSE-DEPENDENT MANNER

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

IMO-9200 DECREASES DISEASE-ASSOCIATED AUTOANTIBODIES IN LUPUS-PRONE MRL/lpr MICE

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

IMO-9200 IMPROVES KIDNEY INTERSTITIAL INFLAMMATION AND GLOMERULOSCLEROSIS IN LUPUS-PRONE MRL/lpr MICE

- In human studies, we have studied the role of IMO-9200 in TLR-mediated signaling pathways and cytokine induction in various in vivo models.
- In vitro studies, we have studied the role of IMO-9200 in TLR-mediated cytokine production in various in vivo models.
- Finally, we have studied the role of IMO-9200 in TLR-mediated autoantibodies production in various in vivo models.

SUMMARY

- IMO-9200 is a novel clinical-stage TLR antagonist.
- IMO-9200 effectively inhibited immune responses mediated through TLRs 7, 8, and 9 in cell-based assays and in mice.
- IMO-9200 DECREASES DISEASE-ASSOCIATED AUTOANTIBODIES IN LUPUS-PRONE MRL/lpr MICE
- IMO-9200 IMPROVES KIDNEY INTERSTITIAL INFLAMMATION AND GLOMERULOSCLEROSIS IN LUPUS-PRONE MRL/lpr MICE