IMO-9200, A NOVEL CLINICAL-STAGE TLR ANTAGONIST FOR THE TREATMENT OF AUTOIMMUNE DISEASES, SUPPRESSES TLR-MEDIATED IMMUNE RESPONSES IN NON-HUMAN PRIMATES FOLLOWING SYSTEMIC ADMINISTRATION

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INTRODUCTION

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Over-activation of Toll-like receptors (TLRs) is implicated in many autoimmune and inflammatory diseases, suggesting TLR antagonism is an important potential treatment approach with broad potential applicability.

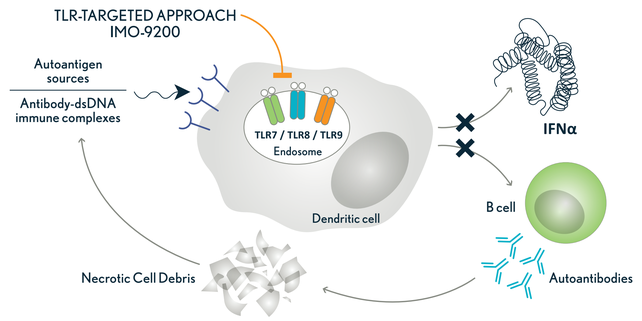
In humans, TLR7 and TLR9 are expressed on plasmacytoid dendritic cells and B cells, and TLR8 is expressed on myeloid dendritic cells. During breakdown of self-tolerance in autoimmune diseases, these TLRs recognize endogenous immune complexes containing self-RNA and -DNA, respectively, leading to pro-inflammatory responses including induction of IFN-α and other cytokines, thereby exacerbating the disease.

A key difference between the cytokine-targeted (antibody) and TLR-targeted approaches is that the latter inhibits the induction but not the constitutive levels of multiple cytokines.

IMO-9200 is a novel clinical-stage antagonist of TLRs 7, 8 and 9 in development for the treatment of autoimmune and inflammatory diseases. Our objective in the present study is to demonstrate IMO-9200 inhibition of TLR-mediated immune responses in a primate model.

ENDOSOMAL TLRs ARE IMPLICATED IN THE PATHOGENESIS OF MULTIPLE AUTOIMMUNE DISEASES

Green NM and Marshak-Rothstein A, Semin Immunol 2011, 23:106-12;
Christensen SR et al, Immunity 2006, 25:417-28;
Jiang W et al, J Invest Derm 2013, 133:1777-84;
Zhu FG et al, Autoimmunity 2013, 46: 419-28;
Suárez-Fariñas M et al, PLoS One 2013, 8:e84634.



METHODS + RESULTS

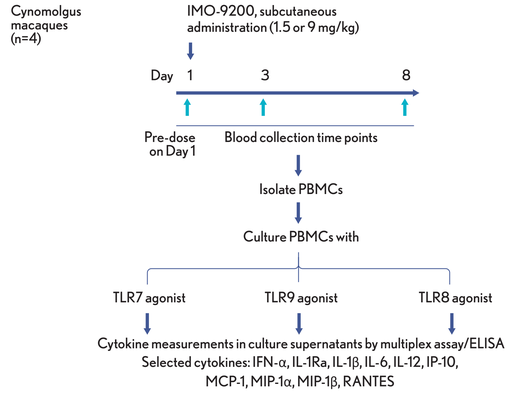
METHODOLOGY

A group of four cynomolgous monkeys received subcutaneous injections of IMO-9200 at 1.5 and 9 mg/kg with a 2-week interval between test article administrations. Blood was collected prior to each IMO-9200 administration and at 24, 48, and 168 hr after each dosing. Whole blood samples were collected into vacutainer tubes containing sodium heparin as anticoagulant and shipped overnight on wet ice. Upon receipt, the samples were processed for peripheral blood mononuclear cell (PBMC) isolation.

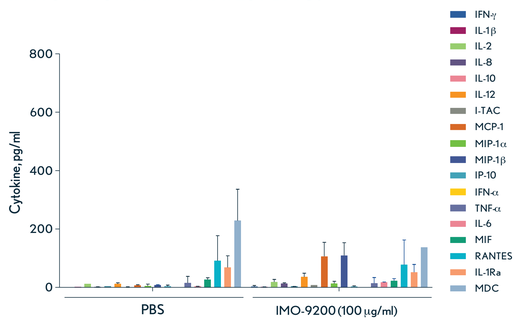
PBMCs were isolated by Ficoll density gradient centrifugation method. PBMCs (1 X 10^6 cells/0.2 ml/well in 96 well plates) were incubated with TLR7 (RNA-based compound, 50 µg/ml) (*Lan T et al, J Med Chem 2009, 52: 6871-6879*), TLR8 (RNA-based compound, 50 µg/ml) (*Lan T et al, Proc Natl Acad Sci USA 2007, 104: 3750-13755*) or TLR9 (DNA-based compound, 3 µg/ml) (*Kandimalla ER et al, Proc Natl Acad Sci USA 2005, 102: 6925-6930*) agonists for 24 hrs. Supernatants were then harvested and stored frozen until assay of cytokines/chemokines.

Cytokine levels in culture supernatants were determined on a Luminex platform using monkey 30-plex magnetic cytokine antibody bead kits (Invitrogen). IFN-α (PBL) and IP-10 (R&D Systems) were measured by ELISA.

NON-HUMAN PRIMATE STUDY PROTOCOL



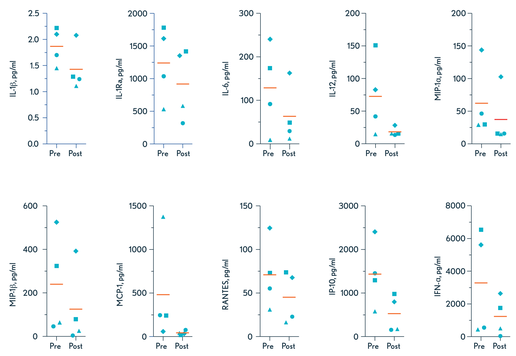
IMO-9200 DOES NOT INDUCE IMMUNE RESPONSES IN NON-HUMAN PRIMATES PBMCs



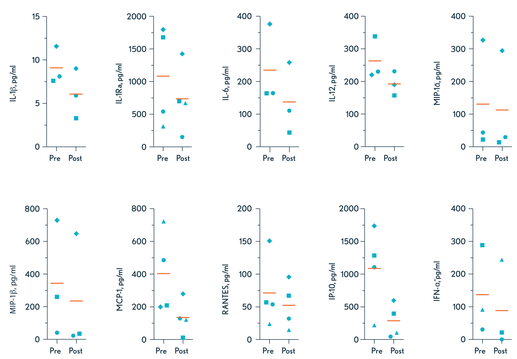
PBMCs were isolated from whole blood and cultured in the presence of PBS or 100 µg/ml IMO-9200 for 24 hrs. Supernatants were analyzed for cytokine levels by Luminex multiplex assay. Mean+/- SD of 2 animals.

IMO-9200 INHIBITS TLR-MEDIATED IMMUNE RESPONSES IN NON-HUMAN PRIMATES

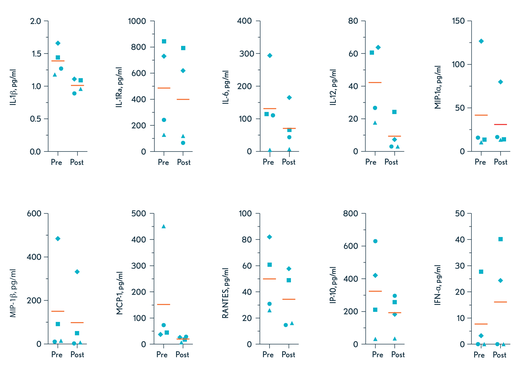
IMO-9200: 1.5 MG/KG



TLR7 Agonist: 50 µg/ml; pre and post 48 hours



TLR8 Agonist: 50 µg/ml; pre and post 48 hours

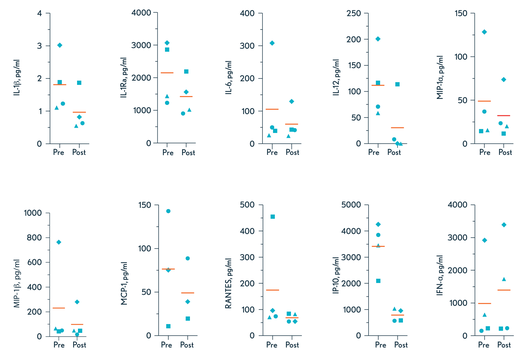


TLR9 Agonist: 3 µg/ml; pre and post 48 hours

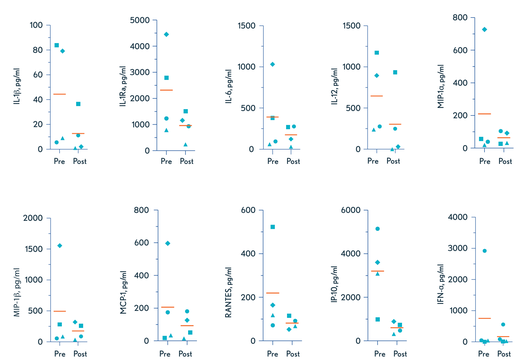
Each symbol represents one animal and red line indicates mean of all animals

IMO-9200 INHIBITS TLR-MEDIATED IMMUNE RESPONSES IN NON-HUMAN PRIMATES

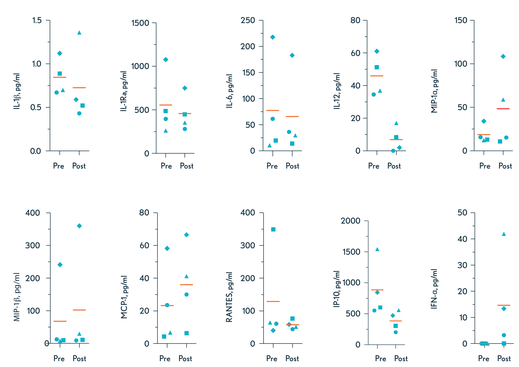
IMO-9200: 9 MG/KG



TLR7 Agonist: 50 µg/ml; pre and post 48 hours



TLR8 Agonist: 50 µg/ml; pre and post 48 hours

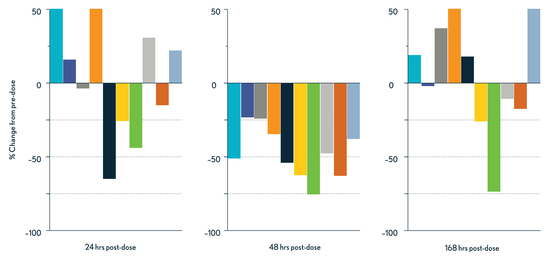


TLR9 Agonist: 3 µg/ml; pre and post 48 hours

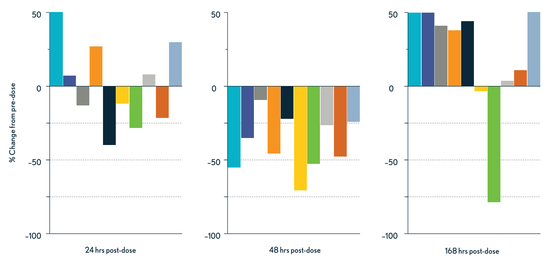
Each symbol represents one animal and red line indicates mean of all animals

TIME COURSE OF IMO-9200 (1.5 MG/KG) INHIBITORY EFFECTS ON TLR AGONIST-INDUCED CYTOKINE SECRETION

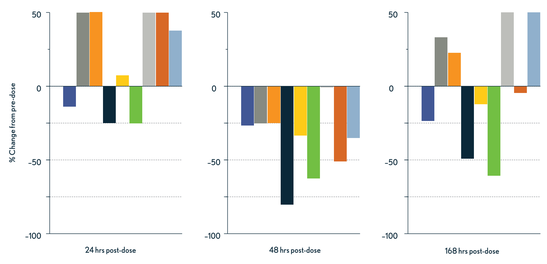
TLR7 AGONIST



TLR8 AGONIST



TLR9 AGONIST



IFN-α IL-1β IL-1Ra IL-6 IL-12
IP-10 MCP-1 MIP-1α MIP-1β RANTES

SUMMARY

- IMO-9200 is a novel clinical-stage antagonist of TLRs 7, 8 and 9
- Systemic administration of IMO-9200 suppressed immune responses mediated through TLRs 7, 8 and 9 in non-human primates
- In this study, IMO-9200 exerted sustained inhibitory effects even at low doses
- IMO-9200 did not induce immune responses by itself
- Results from multiple preclinical studies support clinical development of IMO-9200 as a potential treatment for autoimmune and inflammatory diseases