265 Small Molecule, TLR-4 Ligands as Immonomodulators

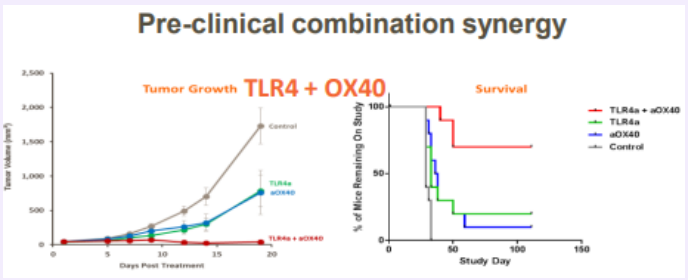
Asset Overview

Product Type	Small molecule
Indication	Oncology, Infectious Diseases
Current Stage	Lead Identification/ optimization
Target(MoA)	TLR4 agonist, NF-kB activation through TLR4/MD2
Brief Description	• Validated means of using TLR-4-specific small molecules as immunomodulatory compositions • Strong ligands are useful as vaccine adjuvants, anticancer agents and immune-stimulants
Organization	University of California, San Diego

Differentiation

□ **Competitiveness landscape of TLR4 agonist**

- TARA-002 (ArTara Therapeutics): Phase II for rare disease, preclinical for others, Cell therapy
- GSK-1795091 (GSK): Phase I for oncology (monotherapy and in combination with immunotherapies in patients with advanced solid tumors), Small molecule (IV), GSK'091 activates key initiating immune pathways and can induce robust anti-tumor efficacy when combined with agonistic antibodies directed against the OX40 receptor in mouse model



- Hp-91 (Batu Biologics): Preclinical for oncology, Synthetic peptide
- Synthetic peptide (University of Oklahoma): Preclinical for infectious disease & oncology
- P-MAPA (Farmabrasilis): TLR2 & 4 agonist, Preclinical for oncology, Small molecule
- CIA-05 (Eyegene): Preclinical for oncology, Polysaccharide
- Biologic (McGill University): Preclinical for drug addiction, Biologic
- ALD-046 (Aluda Pharmaceutical): Preclinical for oncology, Small molecule
- mAb (GigaGen): Discovery for oncology, mAb

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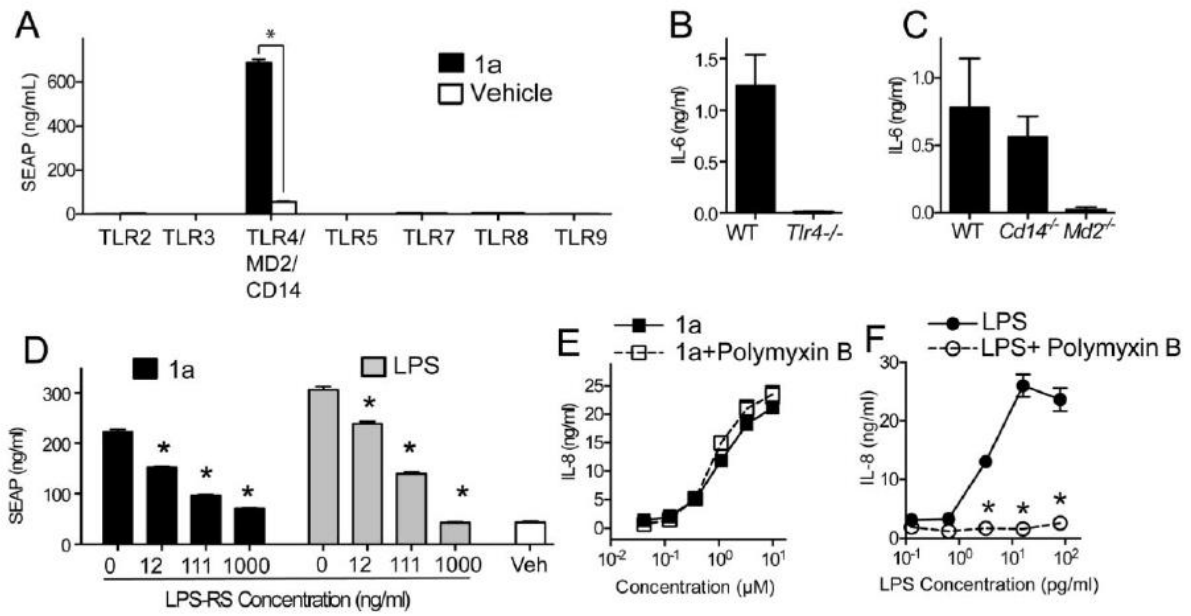
Key Data

1a(2015) is a TLR4 specific ligand that activates NFκB in a TLR4/MD-2-dependent, but CD14-independent manner



(A) Human TLR2, TLR3, TLR4/MD-2/CD14, TLR5, TLR7, TLR8, and TLR9 HEK 293 Blue cells or NFκB/SEAPorter cells were incubated with 1a (10 μM) for 20–24 h, and activation was evaluated by SEAP secretion in the culture supernatants using SEAPorter assay kit. *$p < 0.05$ using Student's t test (B–D) mBMDC prepared from wild type mice or mice genetically deficient for TLR4 (B), MD-2 or CD14 (C) were stimulated with 1a (10 μM). IL-6 levels in the culture supernatant were determined by ELISA. (D) Human TLR4 transfectoma cells were incubated with 10 μM 1a or 10 ng/mL LPS in the presence or absence of TLR4 antagonist LPS-RS (12, 111, 1000 ng/mL). Activation of the TLR4/NFκB pathway was evaluated by SEAP secretion in the culture supernatants. *$p < 0.05$ using one way ANOVA with Dunnett's post hoc testing. (E) Human PBMC were incubated with 1a alone or 1a with polymyxin B (10 μg/mL) overnight. IL-8 in the culture supernatants was measured by ELISA.

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Intellectual Property

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