219 WEHI-345, RIPK2 Inhibitor

Asset Overview

Product Type	Small molecule
Indication	Immunology
Current Stage	Lead optimization
Target(MoA)	Receptor-interacting serine/threonine kinase 2 (RIPK2) inhibitor
Brief Description	• Potent anti-RIPK2 activity (IC_{50} 134nM), high specificity for RIPK2 • Good in vitro and in vivo efficacy (including multiple sclerosis) • Delay in NF-kB transcription factor activation • Bioavailability in mice • No pathology or changes to white blood cells observed at the maximum tolerated
Organization	Walter and Eliza Hall

Differentiation

□ **RIPK2 serine threonine kinase is a key driver of inflammation**

- NOD2 receptors are intracellular sensors of a range of stimuli including peptidoglycan from bacteria
- RIPK2 is an essential mediator of the response to bacterial peptidoglycan
- RIPK2 signaling drives expression of proinflammatory cytokines and type I interferon
- Hyperactivation of NOD2 is a key driver of IBD
- RIPK2 inhibitors have shown efficacy in preclinical models of IBD

□ **Large pharma is developing RIPK2 inhibitors**

- Inhibitor 7 (GSK): small molecule, preclinical for inflammation, high binding affinity for the ATP pocket of RIP2 and inhibition of downstream cytokine production in human whole blood with reduced hERG activity
- GSK-583 (GSK): small molecule (inactive in development, demonstrated effectiveness in blocking downstream NOD2 signaling in cellular models, rodent in vivo models, and human ex vivo disease models but suffered from activity at the hERG and a poor PK/PD profile thereby limiting progression of this analog)
- Small molecule (Oncodesign): preclinical for Crohn's disease, RA, MS, peritonisis (May 2018)

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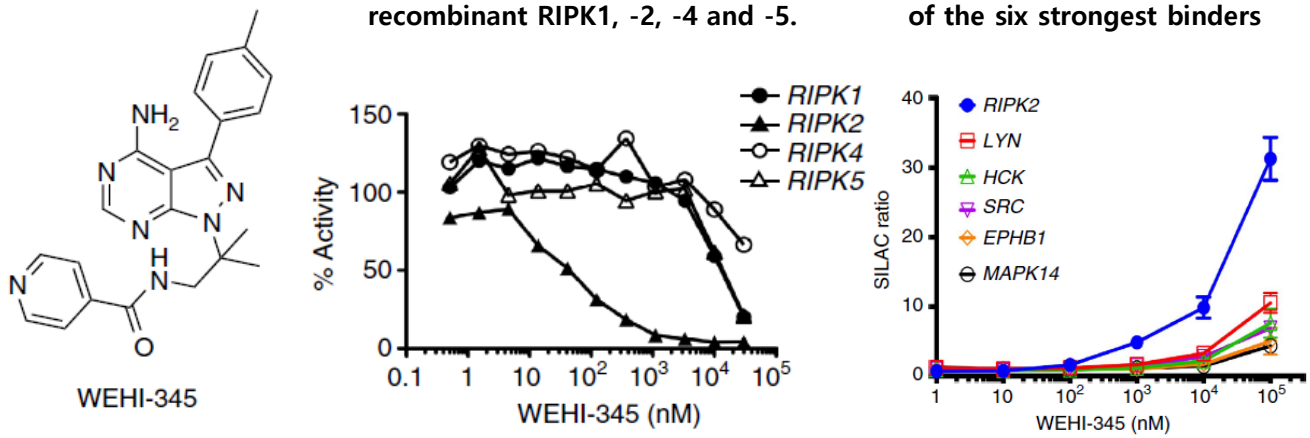
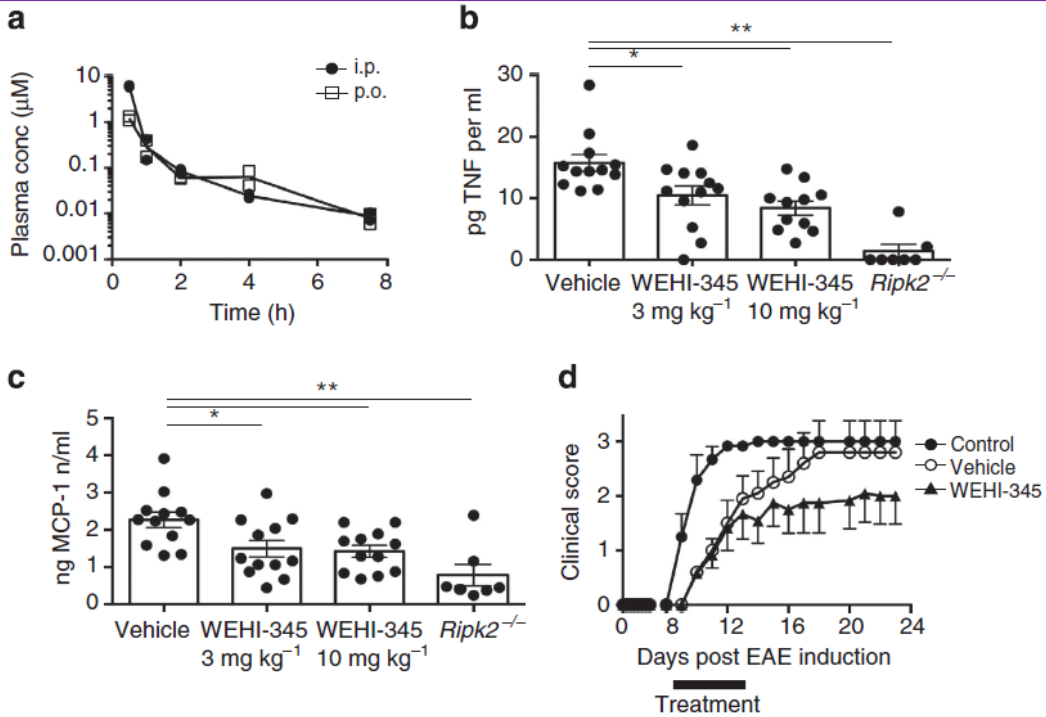
Key Data

WEHI-345 is a selective inhibitor of RIPK2



WEHI-345 inhibits NOD signaling in vivo and has a beneficial effect on an EAE model



(a) Bioavailability of WEHI-345 after intraperitoneal (i.p.) or oral administration in male mice). (b,c) C57BL/6 mice were pretreated for 30 min with either vehicle or WEHI-345 (100 ml, i.p. injection), followed by challenge with MDP (5mgkg-1, i.p. injection) for 4 h. Serum levels of TNF (b) and MCP-1 (c) were determined using enzyme-linked immunosorbent assay. (d) EAE was induced in wild-type C57Bl/6 mice and from day 9 after disease induction, mice were treated twice daily with 20mgkg-1 WEHI-345 for 6 days.

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Intellectual Property

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Application Date	2011.07.08
Status	Registered
Country	US, EP, JP, AU, CA

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