

Validation data for VX-765

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Version 21A25-MM

VX-765 is a pro-drug converted by plasma esterases into an active metabolite, VRT-043198, which potently inhibits caspase-1 and caspase-4. The enzymes, caspase-1 and caspase-4, play an important role in regulating inflammation and pyroptosis, a form of cell death. Notably, inflammasome-activated caspase-1 cleaves and activates the pro-inflammatory cytokines interleukin-1 beta (IL-1 β) and IL-18.

The ability of VX-765 to inhibit caspase-1 was validated using InvivoGen's THP-1/HEK-Blue™ IL-1 β assay. This assay uses the secretion of IL-1 β by THP1-Null2 cells as an indicator of caspase-1 activation and the subsequent NLRP3 inflammasome induction. The NLRP3 inflammasome is an innate immune sensor that is activated by a two-step process; a first signal ('priming') is provided by microbial molecules such as lipopolysaccharide (LPS), while the second signal is provided by a wide array of stimuli including endogenous molecules, such as double-stranded DNA (dsDNA), or crystalline substances such as monosodium urate (MSU) crystals. Treatment with VX-765 inhibited IL-1 β secretion in a dose-dependent manner (Figure 1).

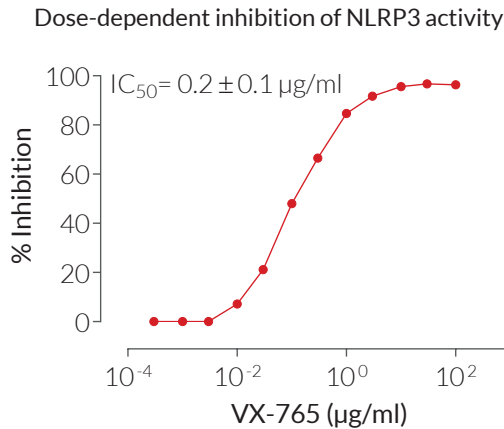


Figure 1: VX-765 inhibits the NLRP3 inflammasome response in a dose-dependent manner.

THP1-Null2 cells, primed with LPS-EK (1 µg/ml for 3 h), were stimulated with MSU (150 µg/ml) and increasing concentrations of VX-765. After overnight incubation, IL-1 β secretion was analyzed by adding 50 µl of supernatant from treated THP1-Null2 cells to HEK-Blue™ IL-1 β cells. IL-1 β -induced activation of NF- κ B was assessed by measuring the levels of SEAP in the supernatant of HEK-Blue™ IL-1 β cells using QUANTI-Blue™ Solution, a SEAP detection reagent, and by reading the optical density (OD) at 655 nm. Data are shown as a percentage (%) inhibition of the maximal response for the ligand with no inhibitor.

TECHNICAL SUPPORT

InvivoGen USA (Toll-Free): 888-457-5873
InvivoGen USA (International): +1 (858) 457-5873
InvivoGen Europe: +33 (0) 5-62-71-69-39
InvivoGen Hong Kong: +852 3622-3480
E-mail: info@invivogen.com