# Validation data for VX-765

https://www.invivogen.com/vx-765

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Version 22F07-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-1β) and IL-18.
The ability of VX-765 to inhibit caspase-1 was validated using InvivoGen's THP-1/HEK-Blue™ IL-1β assay. This assay uses the secretion of IL-1β 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-1β secretion in a dose-dependent manner **(Figure 1)**.

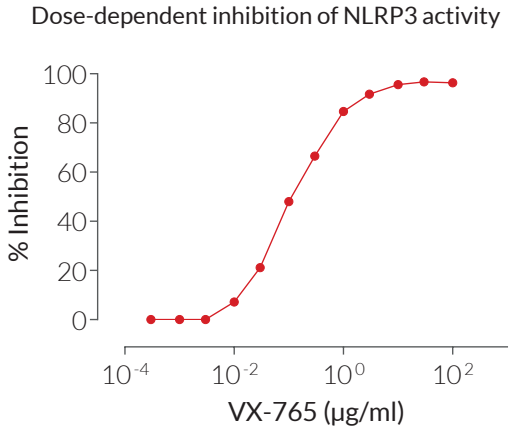


**Figure 1: VX-765 inhibits the NLRP3 inflammasome response in a dose-dependent manner.**
THP1-Null2 cells, primed with LPS-EK (1 µg/ml for 3 h), were stimulated with MSU (150 µg/ml) and increasing concentrations of VX-765. After overnight incubation, IL-1β secretion was analyzed by adding 50 µl of supernatant from treated THP1-Null2 cells to HEK-Blue™ IL-1β cells. IL-1β-induced activation of NF-κB was assessed by measuring the levels of SEAP in the supernatant of HEK-Blue™ IL-1β cells using QUANTI-Blue™ Solution, a SEAP detection reagent, and by reading the optical density (OD) at 655 nm. Data are shown as percentage (%) inhibition.


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