Validation data for RU.521

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Version 22F07-MM

RU.521 is described as a small molecule inhibitor of cGAS (cyclic GMP-AMP synthase, cGAMP synthase). The activity of this inhibitor has been tested using the murine macrophage RAW-Lucia™ ISG cells which endogenously express multiple cytosolic DNA sensors (CDSs), including cGAS. These cells were stably transfected with an interferon regulatory factor (IRF)-inducible secreted Lucia luciferase reporter gene.
Stimulation of RAW-Lucia™ ISG cells with CDS ligands, such as cytosolic double-stranded DNA (dsDNA), leads to a significant IRF response. This response is inhibited in a dose-dependent manner by RU.521 (Figure 1). RU.521 displays a clear inhibitory effect on cGAS activation by cytosolic dsDNA and the cGAS agonist G3-YSD (Y-form DNA; Figure 2).

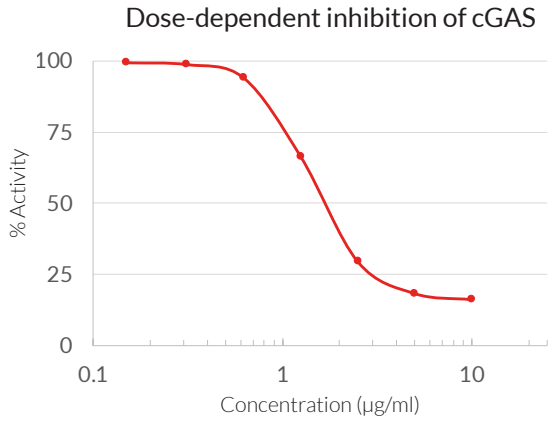

Figure 1: Effect of RU.521 on the response of RAW-Lucia™ ISG cells to cytosolic dsDNA. RAW-Lucia™ ISG cells were incubated with 1 µg/ml of cytosolic dsDNA (plasmid DNA delivered intracellularly using cationic lipid transfection) and increasing concentrations of RU.521. After overnight incubation, the IRF response was assessed by determining Lucia luciferase activity in the supernatant using QUANTI-Luc™. Data are shown as percentage (%) activity.

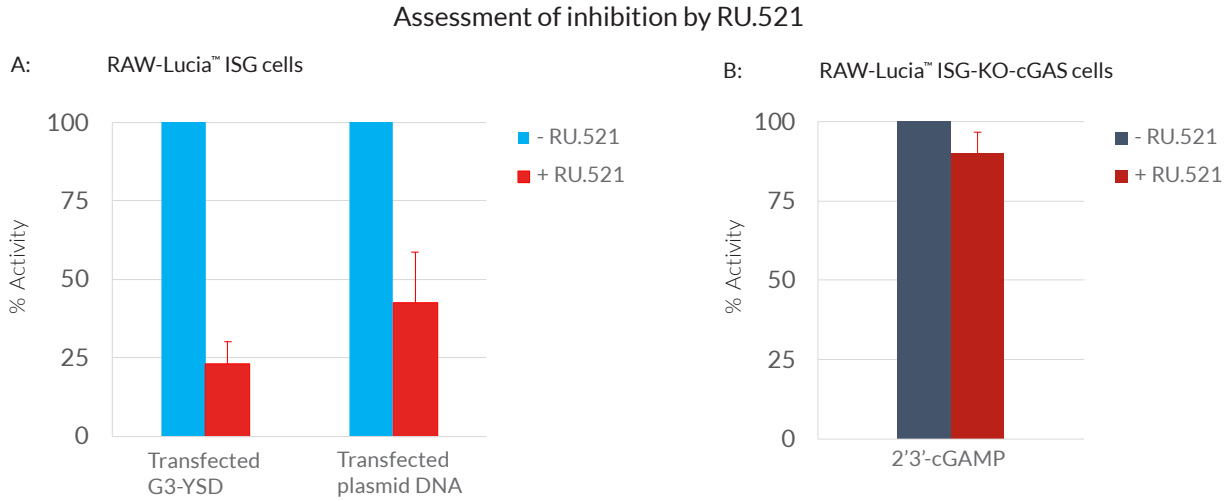

Figure 2A: RU.521 primarily inhibits cGAS activity. RAW-Lucia™ ISG cells were incubated with 1 µg/ml of cytosolic G3-YSD (Y-form DNA) and plasmid DNA in the presence or absence of 2.5 µg/ml of RU.521. G3-YSD and the plasmid DNA were delivered into the cytoplasm using cationic lipid transfection. **B:** RAW-Lucia™ ISG-KO-cGAS cells were incubated with 10 µg/ml of 2'3'-cGAMP in the presence or absence of 2.5 µg/ml of RU.521. After overnight incubation, the IRF response was assessed using QUANTI-Luc™ and expressed as percentage (%) activity.

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