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Small Molecule Inhibitors of TREM2/Gal3 Interaction as Therapies for Alzheimer's Disease

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Abstract : Galectin-3 has been identified as a critical player in driving the neuroinflammatory responses in Alzheimer's disease (AD). A key feature of this function of galectin-3 is associated with its interaction with the triggering receptor expressed on myeloid cells-2 (TREM2). Herein, we report a high-throughput screening (HTS) platform that can be used for the identification of inhibitors of TREM2 and galectin-3 interaction. We have utilized this HTS assay to screen a focused library of compounds optimized for central nervous system (CNS)-related diseases. MG-257 was identified from this screen as the first example of a small molecule that can attenuate TREM2 signaling based on its high affinity to galectin-3 (endogenous ligand of TREM2). Remarkably, MG-257 reduced the levels of proinflammatory cytokines in activated microglial cells, which highlights its ability to inhibit the neuroinflammatory response associated with AD.

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