Ibudilast

National Cancer Institute

Source

National Cancer Institute. Ibudilast. NCI Thesaurus. Code C65876.

An orally bioavailable inhibitor of cyclic nucleotide phosphodiesterase (PDE), mainly PDE-3, -4, -10, and -11, with anti-(neuro)inflammatory, vasorelaxant, bronchodilator, analgesic, neuroprotective and potential anti-tumor activities. Ibudilast (IBD) is able to cross the blood-brain barrier (BBB). Upon administration, IBD exerts its potential anti-tumor activity against glioblastoma multiforme (GBM) cells by inhibiting PDE-4 and the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF), which results in a decrease in MIF, its receptor CD74, and AKT expression, and attenuates the immunosuppressive properties of monocytic myeloid-derived suppressor cells (MDSCs) and reduces T-regulatory cells (Tregs). This causes GBM cell apoptosis and inhibits GBM cell proliferation. In addition, IBD reduces, through its inhibitory effect on various PDEs, the production of certain pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1beta, leukotriene B4, and tumor necrosis factor-alpha (TNF-a). IBD also upregulates the anti-inflammatory cytokine (IL-10), and promotes the production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-4 (NT-4). It also blocks toll-like receptor-4 (TLR-4), inhibits nitric oxide (NO) synthesis and reduces the level of reactive oxygen species (ROS). It also prevents platelet aggregation, causes cerebral vasodilation, bronchial smooth muscle relaxation, and improves cerebral blood flow. In addition, IBD attenuates the PDE-mediated activation of glial cells and abrogates PDE-mediated neuroinflammation and neurodegeneration. MIF is secreted by cancer stem cells (CSCs) and is highly expressed within GBM and plays a key role in tumor cell proliferation. Co-expression of MIF and CD74 in GBM is associated with poor patient survival.