The cGAS-cGAMP-STING pathway plays a crucial role in promoting anti-tumor immunity. A medicinal chemistry effort led to the identification of GBD-09259, a small molecule. Adapted from Carozza et al. 2019.

CD73 suppresses immune cell function (cGAMP, ATP and NAD+ also generates AMP, which upon conversion to adenosine by ENPP1 inhibitors may demonstrate improved safety profiles vs. STING agonists as STING agonists showed detrimental effects on immune cells which may compromise anti-tumor efficacy.

An ENPP1 inhibitor may boost STING activation and STING Agonists and Confers Anti-Tumor Efficacy in Combination With Other Therapies in Syngeneic Tumor Models. An Orally Bioavailable ENPP1-Selective Inhibitor Demonstrates Superior Immune Preservation Effects Over STING Agonists.

Background

- The GDB-09259 enhanced the efficacy of anti-PD1 and cisplatin in multiple syngeneic tumor models.
- GDB-09259 demonstrated superior immune protection compared with STING agonists.
- GDB-09259 is a potent and selective ENPP1 inhibitor that stimulates IFNβ production without negatively impacting proliferation or survival of human T cells.

Summary and Conclusions

GDB-09259 is a potent and selective ENPP1 inhibitor that stimulates IFNβ production without negatively impacting proliferation or survival of human T cells. GDB-09259 enhanced the efficacy of anti-PD1 and cisplatin in multiple syngeneic tumor models. GDB-09259 demonstrated superior immune protection compared with STING agonists. GDB-09259 is a potential candidate suitable for clinical development.

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References