Product Data Sheet

Product Name: PF-06446846
Cat. No.: GC25727

Chemical Properties

Cas. No.	1632250-49-7		
Formula	C22H20ClN7O	M.Wt	433.89
Solubility	DMSO: 87 mg/mL (200.51 mM);Water: Insoluble;Ethanol: 87 mg/mL (200.51 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	PF-06446846		

Protocol

Cell experiment [1]:

Cell lines	OVCAR3, OVCAR3cis, A2780, A2780cis, JHOS2, Kuramochi, Ovsaho, COV362, and HeLa cells (human ovarian cancer cell lines and cervical carcinoma cell line)
Preparation Method	Cells were cultured in RPMI 1640 or DMEM supplemented with 10-20% fetal bovine serum (FBS) and maintained at 37°C, 5% CO_2. Cells were treated with PF-06446846 at 100 for 48 hours.
Reaction Conditions	100μM; 48h

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Applications	PF-06446846 significantly impaired ovarian cancer cell survival, with HeLa, OVCAR3, and OVCAR3cis cells showing reduced viability, while PCSK9-negative JHOS2 cells exhibited minimal sensitivity. PF-06446846 treatment also induced robust phosphorylation of AKT, ERK1/2, and MEK1/2 upon PCSK9 overexpression, indicating a pro-survival role of PCSK9 in ovarian cancer cells.

Animal experiment [2]:

Animal models	615-line mice and C57BL/6 mice
Preparation Method	MFC gastric cancer cells were subcutaneously implanted into 615-line mice. B16F10-OVA melanoma cells were subcutaneously implanted into C57BL/6 mice. Mice were intraperitoneally administered PF-06446846 (5mg/kg) every other day for 10-18 days. Mice were sacrificed at the treatment endpoint for tumor analysis.
Dosage form	5mg/kg; i.p.; Every other day for 10-18 injections.
Applications	PF-06446846 significantly suppressed tumor growth in both gastric cancer and melanoma models, reducing tumor volumes and weights. The inhibitor upregulated MHC-II expression on dendritic cells and tumor cells in the tumor microenvironment, enhanced $CD8^+$ T cell infiltration and activation, and improved the anti-tumor efficacy of OVA-II peptide vaccines when used in combination therapy.

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References:
[1] Jacome Sanz D, Raivola J, Karvonen H, et al. Evaluating Targeted Therapies in Ovarian Cancer Metabolism: Novel Role for PCSK9 and Second Generation mTOR Inhibitors. Cancers (Basel). 2021 Jul 24;13(15):3727.
[2] Wang H, Zhang X, Zhang Y, et al. Targeting PCSK9 to upregulate MHC-II on the surface of tumor cells in tumor immunotherapy. BMC Cancer. 2024 Apr 10;24(1):445.

Background

PF-06446846 is an orally active proprotein convertase subtilisin/kexin type 9 (PCSK9) translation inhibitor[1-2]. PF-06446846 selectively inhibits PCSK9 synthesis by inducing ribosomal stalling near codon 34. PF-06446846 can be used in research related to atherosclerosis and cancer[3-4].

In vitro, in a HepG2 and AFP-specific TCR-T cell co-culture system, PF-06446846 (10μM) treatment of TCR-T cells for 12 hours, PF-06446846 enhanced the killing activity of TCR-T cells against hepatocellular carcinoma cells, downregulated PD-1 expression on the T cell surface, and promoted $CD8^+$ T cell activation by upregulating the LDLR-mediated mTORC1 signaling pathway[5]. PF-06446846 (100μM) pretreatment of OVCAR3 and HeLa cells for 48 hours, PF-06446846 significantly inhibited PCSK9 expression and reduced cell survival[6].

In vivo, in the MFC gastric cancer model using 615-line male mice, PF-06446846 (5mg/kg/day) was administered intraperitoneally from day 2 after tumor inoculation (every other day for a total of 10 injections). PF-06446846 significantly inhibited tumor

growth and reduced tumor weight, while upregulating MHC-II expression on dendritic cells and tumor cells in the tumor microenvironment and enhancing $CD8^+$ T cell infiltration and functional activation[7]. In the B16F10-OVA melanoma model in C57BL/6 mice, PF-06446846 (5mg/kg) was administered intraperitoneally from day 2 after tumor inoculation (every other day for a total of 8 injections). When used in combination with the OVA-II long peptide vaccine (10μg/mouse; administered subcutaneously from day 3), PF-06446846 significantly enhanced the monotherapeutic anti-tumor efficacy of the OVA-II vaccine, achieving superior tumor control[8].

References:

[1] Liaud N, Horlbeck MA, Gilbert LA, et al. Cellular response to small molecules that selectively stall protein synthesis by the ribosome. PLoS Genet. 2019 Mar 15;15(3):e1008057.
[2] Li W, Ward FR, McClure KF, et al. Structural basis for selective stalling of human ribosome nascent chain complexes by a drug-like molecule. Nat Struct Mol Biol. 2019 Jun;26(6):501-509.
[3] Aspnes GE, Coffey SB, Darout E, et al. Small molecule inhibitors of PCSK9. SAR investigations of head and amine groups. Bioorg Med Chem Lett. 2023 Aug 15;92:129394.
[4] Zhang D, Li Q, Chen X, et al. An Injectable Hydrogel to Modulate T Cells for Cancer Immunotherapy. Small. 2022 Aug;18(32):e2202663.
[5] Xu W, Hu M, Lu X, et al. Inhibition of PCSK9 enhances the anti-hepatocellular carcinoma effects of TCR-T cells and anti-PD-1 immunotherapy. Int J Biol Sci. 2024 Jul 15;20(10):3942-3955.
[6] Jacome Sanz D, Raivola J, Karvonen H, et al. Evaluating Targeted Therapies in Ovarian Cancer Metabolism: Novel Role for PCSK9 and Second Generation mTOR Inhibitors. Cancers (Basel). 2021 Jul 24;13(15):3727.
[7] Wang H, Zhang X, Zhang Y, et al. Targeting PCSK9 to upregulate MHC-II on the surface of tumor cells in tumor immunotherapy. BMC Cancer. 2024 Apr 10;24(1):445.
[8] Lintner NG, McClure KF, Petersen D, et al. Selective stalling of human translation through small-molecule engagement of the ribosome nascent chain. PLoS Biol. 2017 Mar 21;15(3):e2001882.

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