产品名称：Vismodegib(GDC-0449)
产品别名：Vismodegib；维莫德吉

生物活性：

Description	Vismodegib (GDC-0449) is an orally active hedgehog pathway inhibitor with an IC_{50} of 3 nM. It also inhibits P-gp, ABCG2 with IC_{50} values of 3.0 μM and 1.4 μM, respectively.
IC_{50} & Target	IC50: 3 nM (hedgehog), 3.0 μM (P-gp), 1.4 μM (ABCG2)
In Vitro	Vismodegib (HhAntag691) is an ABCG2 inhibitor and can increase the effective intracellular concentration of NSC 279836, another ABCG2 substrate, through blocking its export in HEK293 cells. Vismodegib (HhAntag691, 10 μM), resensitizes MDCKII/Pgp cells and MDCKII/MRP1 cells to NSC757 treatment[2]. Vismodegib (25 μM or 50 μM) concentration dependently inhibits HCC and H1339 cells[3].
In Vivo	Vismodegib is a novel small molecule HPI, often used for clinical trials[1]. Vismodegib (0.3 to 75 mg/kg, p.o.) is highly efficacious in medulloblastoma allograft tumors. Vismodegib (> 46 mg/kg, p.o.) causes growth delay in patient-derived colorectal xenografts[4].

Solvent&Solubility

In Vitro:

DMSO : ≥ 50 mg/mL (118.68 mM)

Ethanol : 2.86 mg/mL (6.79 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3736 mL	11.8680 mL	23.7361 mL
5 mM	0.4747 mL	2.3736 mL	4.7472 mL
10 mM	0.2374 mL	1.1868 mL	2.3736 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (5.93 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.93 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)

Solubility: 2.5 mg/mL (5.93 mM); Suspended solution; Need ultrasonic and warming

此方案可获得 2.5 mg/mL (5.93 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理

	盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.93 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.93 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Scales SJ, et al. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. Trends Pharmacol Sci. 2009, 30(6), 303-312. [2]. Zhang Y, et al. Hedgehog pathway inhibitor HhAntag691 is a potent inhibitor of ABCG2/BCRP and ABCB1/Pgp. Neoplasia. 2009, 11(1), 96-101. [3]. Tian F, et al. The hedgehog pathway inhibitor GDC-0449 alters intracellular Ca^{2+} homeostasis and inhibits cell growth in NSC 119875-resistant lung cancer cells. Anticancer Res. 2012, 32(1), 89-94. [4]. Wong H, et al. Pharmacokinetic-pharmacodynamic analysis of vismodegib in preclinical models of mutational and ligand-dependent Hedgehog pathway activation. Clin Cancer Res. 2011, 17(14), 4682-4692. [5]. Elhenawy AA, et al. Possible antifibrotic effect of GDC-0449 (Vismodegib), a hedgehog-pathway inhibitor, in mice model of Schistosoma-induced liver fibrosis. Parasitol Int. 2017 Oct;66(5):545-554. [6]. Ma W, et al. Reduced Smoothened level rescued Aβ-induced memory deficits and neuronal inflammation in animal models of Alzheimer's disease. J Genet Genomics. 2018 May 20;45(5):237-246.

实验参考：

Cell Assay	When MTT assay is performed, an MTT reagent is added to each well to a final concentration of 150 μg/mL, and the cells are incubated for 1 to 2 hours at 37°C. The medium is then replaced with DMSO to dissolve the reaction product. Absorbance at 570 nm is quantified using a spectra MAX 340pc plate reader. For the XTT assay, 1 mg/mL XTT is mixed with 0.025 mM PMS, and 50 μL of the mixture is added to each well and incubated for 4 hours at 37°C. After the plates are mixed on a plate shaker, absorbance at 450 nm is measured. All results are normalized to a percentage of absorbance obtained in controls. [2]
Animal Administration	Tumor-bearing mice are distributed into tumor volume-matched cohorts when the tumors reache between 200 and 350 mm^3. The vismodegib-resistant medulloblastoma allograft, sg274, is developed by intermittent suboptimal dosing of a $Ptch^{+/-}$, $p53^{-/-}$medulloblastoma allograft. Vismodegib is formulated as a suspension in 0.5% methyl-cellulose, 0.2% tween-80 (MCT), and is administered orally. Tumor volumes are determined using digital calipers using the formula (L×W×W)/2. Tumor growth inhibition (%TGI) is calculated as the percentage of the area under the fitted curve (AUC) for the respective dose group per day in relation to the vehicle, such that %TGI=100×1-(AUCtreatment/day)/(AUCvehicle/day). [2]
References	[1]. Scales SJ, et al. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. Trends Pharmacol Sci. 2009, 30(6), 303-312. [2]. Zhang Y, et al. Hedgehog pathway inhibitor HhAntag691 is a potent inhibitor of ABCG2/BCRP and ABCB1/Pgp. Neoplasia. 2009, 11(1), 96-101. [3]. Tian F, et al. The hedgehog pathway inhibitor GDC-0449 alters intracellular Ca^{2+} homeostasis and inhibits cell growth in NSC 119875-resistant lung cancer cells. Anticancer Res. 2012, 32(1),

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[4]. Wong H, et al. Pharmacokinetic-pharmacodynamic analysis of vismodegib in preclinical models of mutational and ligand-dependent Hedgehog pathway activation. Clin Cancer Res. 2011, 17(14), 4682-4692.

[5]. Elhenawy AA, et al. Possible antifibrotic effect of GDC-0449 (Vismodegib), a hedgehog-pathway inhibitor, in mice model of Schistosoma-induced liver fibrosis. Parasitol Int. 2017 Oct;66(5):545-554.

[6]. Ma W, et al. Reduced Smoothened level rescued Aβ-induced memory deficits and neuronal inflammation in animal models of Alzheimer's disease. J Genet Genomics. 2018 May 20;45(5):237-246.