产品名称：TIC10
产品别名：ONC-201

生物活性：

Description	TIC10 is a potent, orally active, and stable tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) inducer which acts by inhibiting Akt and ERK, consequently activating Foxo3a and significantly inducing cell surface TRAIL. TIC10 can cross the blood-brain barrier.
IC_{50} & Target	TRAIL
In Vitro	TIC10 transcriptionally induces TRAIL in a p53-independent manner and crosses the blood-brain barrier[1]. TIC10 induces a sustained up-regulation of TRAIL in tumors and normal cells that may contribute to the demonstrable antitumor activity of TIC10[1]. TIC10 inactivates kinases Akt and extracellular signal-regulated kinase (ERK), leading to the translocation of Foxo3a into the nucleus, where it binds to the TRAIL promoter to up-regulate gene transcription[1]. TIC10 is an efficacious antitumor therapeutic agent that acts on tumor cells and their micro-environment to enhance the concentrations of the endogenous tumor suppressor TRAIL[1]. TIC10 also causes a down-regulation of the total expression of ERK[1].
In Vivo	In DLD-1 colon cancer xenografts, TIC10 induces tumor stasis at 1 week after treatment, whereas TRAIL-treated tumors progress after a single dose. A single dose of TIC10 also induces a sustained regression of the SW480 xenograft and is equally effective when delivered by intraperitoneal or oral route, suggesting favorable oral bioavailability for TIC10. Titration of a single oral dose of TIC10 in the HCT116 xenograft model reveals sustained antitumor efficacy at 25 mg/kg. Exposure to oral TIC10 at 25 mg/kg weekly for 4 weeks in immunocompetent mice does not cause any changes in selected serum chemistry markers. The same oral dosing schedule is applied to Eμ-myc transgenic mice, which spontaneously develop meta-static lymphoma from weeks 9 to 12 of age, and TIC10 significantly (P=0.00789) prolongs the survival of these mice by 4 weeks[1].
Solvent&Solubility	***In Vitro:*** **DMSO : 31.25 mg/mL (80.86 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5874 mL	12.9369 mL	25.8739 mL
	5 mM	0.5175 mL	2.5874 mL	5.1748 mL
	10 mM	0.2587 mL	1.2937 mL	2.5874 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 (6.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.47 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 (6.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.47 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 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 (6.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.47 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]. Allen JE, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. Sci Transl Med. 2013 Feb 6;5(171):171ra17.

实验参考：

Cell Assay	Floating and adherent cells are analyzed on a Coulter-Beckman Elite Epics cytometer. For surface TRAIL experiments, adherent cells are harvested by brief trypsinization, fixed in 4% paraformaldehyde in phosphate-buffered saline (PBS) for 20 min, incubated with an anti-TRAIL antibody at 1:250 overnight, washed and incubated with anti-rabbit Alexa Fluor 488 for 30 min, and analyzed. Cells are gated on forward and side scatter to eliminate debris and dead cells from the analysis. Surface TRAIL data are expressed as median fluorescence intensity relative to that of control samples unless indicated otherwise. Surface DR5 is analyzed similarly with an antibody from Imgenex. For sub-G_1content and cell cycle profile analysis, all cells are pelleted and ethanol-fixed, followed by staining with propidium iodide in the presence of RNase. Cell viability assays are carried out in 96-well black-walled clear-bottom plates with CellTiter-Glo[1].
Animal Administration	Mice[1] For subcutaneous xenografts, 4- to 6-week-old female athymic nu/nu mice are inoculated with 1×10^6 cells ($2.5\times10^6$for T98G) of the indicated cell lines in each rear flank as a 200-μL suspension of 1:1 Matrigel (BD)/PBS. All subcutaneous tumors are allowed to establish for 1 to 4 weeks after injection until reaching a volume of ~125 mm^3before treatment initiation. All intraperitoneal and intravenous injections are given at a total volume of 200 μL. Oral formulations of TIC10 are administered by oral gavage and given as a 200 μL suspension containing 20% Cremophor EL, 10% DMSO, and 70% PBS. Tumors are monitored with digital calipers at indicated time points. All subcutaneous tumors are allowed to establish for 1-4 weeks post-injection until reaching a volume of ~125 mm^3before treatment initiation. Relief of tumor burden is monitored for 3 weeks after disappearance of the tumor and confirmed by visual inspection after euthanasia.
References	[1]. Allen JE, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. Sci Transl Med. 2013 Feb 6;5(171):171ra17.