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产品名称：Lenalidomide (hemihydrate)
产品别名：来那度胺半水合物；CC-5013 hemihydrate

生物活性：

Description	Lenalidomide hemihydrate (CC-5013 hemihydrate) is a derivative of Thalidomide and an orally active immunomodulator. Lenalidomide hemihydrate (CC-5013 hemihydrate) is a ligand of ubiquitin E3 ligase cereblon (CRBN), and it causes selective ubiquitination and degradation of two lymphoid transcription factors, IKZF1 and IKZF3, by the CRBN-CRL4 ubiquitin ligase. Lenalidomide hemihydrate (CC-5013 hemihydrate) specifically inhibits growth of mature B-cell lymphomas, including multiple myeloma, and induces IL-2 release from T cells[1][2].
IC_{50} & Target	Cereblon
In Vitro	Lenalidomide is potent in stimulating T cell proliferation and IFN-γ and IL-2 production. Lenalidomide has been shown to inhibit production of pro inflammatory cytokines TNF-α, IL-1, IL-6, IL-12 and elevate the production of anti-inflammatory cytokine IL-10 from human PBMCs. Lenalidomide downregulates the production of IL-6 directly and also by inhibiting multiple myeloma (MM) cells and bone marrow stromal cells (BMSC) interaction, which augments the apoptosis of myeloma cells[2]. Dose-dependent interaction with the CRBN-DDB1 complex is observed with Thalidomide, Lenalidomide and Pomalidomide, with IC_{50} values of ~30 μM, ~3 μM and ~3 μM, respectively, These reduced CRBN expression cells (U266-$CRBN_{60}$ and U266-$CRBN_{75}$) are less responsive than the parental cells to antiproliferative effects Lenalidomide across a dose-response range of 0.01 to 10 μM[3]. Lenalidomide, a thalidomide analog, functions as a molecular glue between the human E3 ubiquitin ligase cereblon and CKIα is shown to induce the ubiquitination and degradation of this kinase, thus presumably killing leukemic cells by p53 activation[5].
In Vivo	The toxicity of Lenalidomide doses up to 15, 22.5, and 45 mg/kg via IV, IP, and PO routes of administration. Limited by solubility in our PBS dosing vehicle, these maximum achievable Lenalidomide doses are well tolerated with the exception of one mouse death (of four total dosed) at the 15 mg/kg IV dose. Notably, no other toxicities are observed in the study at IV doses of 15 mg/kg (n=3) or 10 mg/kg (n=45) or at any other dose level through IV, IP, and PO routes[4].

In Vitro:

DMSO : 50 mg/mL (**186.38 mM;** Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.7276 mL	18.6379 mL	37.2759 mL
5 mM	0.7455 mL	3.7276 mL	7.4552 mL
10 mM	0.3728 mL	1.8638 mL	3.7276 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:

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Solvent&Solubility	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 (9.32 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (9.32 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 (9.32 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (9.32 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 (9.32 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (9.32 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]. Omran A, et al. Effects of MRP8, LPS, and lenalidomide on the expressions of TNF-α , brain-enriched, and inflammation-related microRNAs in the primary astrocyte culture. ScientificWorldJournal. 2013 Sep 21;2013:208309. [2]. Minzel W, et al. Small Molecules Co-targeting CKIα and the Transcriptional Kinases CDK7/9 Control AML in Preclinical Models. Cell. 2018 Sep 20;175(1):171-185.e25. [3]. Kotla V, et al. Mechanism of action of lenalidomide in hematological malignancies. J Hematol Oncol. 2009 Aug 12;2:36. [4]. Lopez-Girona A, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia. 2012 Nov;26(11):2326-35. [5]. Rozewski DM, et al. Pharmacokinetics and tissue disposition of lenalidomide in mice. AAPS J. 2012 Dec;14(4):872-82.

实验参考：

Cell Assay	Cell lines NCI-H929 and U266, and DF15 cells are grown in RPMI-I640 medium containing 10% (V/V) heat-inactivated fetal bovine serum supplemented with 2 mM glutamine. To produce Lenalidomide resistant cell lines, NCI-H929 cells are treated continuously (fresh Lenalidomide is added every 3-4 days) with control (final 0.1% DMSO) or low-dose Lenalidomide (1 μM) for 2 months until the proliferation of cells is no longer inhibited by Lenalidomide (1 μM), as determined by cell viability (Vi-cell XR cell viability analyzer), cell proliferation by flow cytometry and cell cycle

	analysis (propidium iodide staining). After acquisition of resistance to 1 μM, the resistant H929 cell lines are treated with Lenalidomide (10 μM) for a further 4 months. After this period of time, the cell cultures achieved fully establish resistance up to high-dose Lenalidomide (30 μM). Prior to the experiments described here, H929 Lenalidomide-resistant cells are taken out of culture with compounds for 5-7 days before use[3].
Animal Administration	Mice[4] Imprinting control region (ICR) mice 8-10 weeks of age are used. Lenalidomide is incompletely soluble at 3.5 mg/mL and above in PBS containing 1% HCl, as visible particulates remained after thorough mixing. Therefore 3 mg/mL is selected as the maximum dosing solution concentration (with no visible particulates). Single, individual mice are initially dosed with 3, 10, or 15 mg/kg IV; 4.5, 15, or 22.5 mg/kg IP; and 9, 30, or 45 mg/kg PO. Additional mice (n=4) are then evaluated at the maximum dose achievable by volume and solubility of Lenalidomide in the dosing solution. All mice are monitored closely for 1 h and re-evaluated for toxicities 3, 6, and 24 h postdose.
References	[1]. Omran A, et al. Effects of MRP8, LPS, and lenalidomide on the expressions of TNF-α , brain-enriched, and inflammation-related microRNAs in the primary astrocyte culture. ScientificWorldJournal. 2013 Sep 21;2013:208309. [2]. Minzel W, et al. Small Molecules Co-targeting CKIα and the Transcriptional Kinases CDK7/9 Control AML in Preclinical Models. Cell. 2018 Sep 20;175(1):171-185.e25. [3]. Kotla V, et al. Mechanism of action of lenalidomide in hematological malignancies. J Hematol Oncol. 2009 Aug 12;2:36. [4]. Lopez-Girona A, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia. 2012 Nov;26(11):2326-35. [5]. Rozewski DM, et al. Pharmacokinetics and tissue disposition of lenalidomide in mice. AAPS J. 2012 Dec;14(4):872-82.