KDDF
Korea Drug Development Fund

Asset #43
Weill Cornell Medicine

Inhibitors of MALT1 for the Treatment of Lymphomas

Therapeutic Area	Oncology	**Indications**	Diffuse Large B-Cell Lymphoma
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

- Mucosa-associated lymphoid tissue lymphoma translocation 1 (MALT1) is a critical mediator of B-Cell receptor signaling
- MALT1 mediates NF-κB signaling by functioning as a scaffold protein and protease to trigger downstream signals
- 70% of patients with activated B cell-like (ABC) DLBCL show a gain or amplification of MALT1
- The protease activity of MALT1 has been shown to be essential for the survival of ABC DLBCL cell lines that rely on constitutive NF-κB signaling
- Unmet Need: Selective MALT1 inhibitors as lead therapeutic candidates for ABC DLBCL

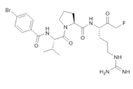
Technology Advantages

- MALT1's pivotal role in ABC DLBCL and its potential as a therapeutic target drove the development of effective substrate-mimetic compounds, suppressing tumor cells in vitro and in vivo.
- Reduction in serum IL-10 levels correlated with drug pharmacokinetics and MALT1 inhibition, suggesting a potential pharmacodynamic biomarker. MALT1 inhibition also revealed insights into JAK/STAT signaling and immune response modulation. Both covalent and allosteric inhibitors showed promising potency and selectivity for further development.

Key Data

Three promising approaches for therapeutic MALT1 inhibition

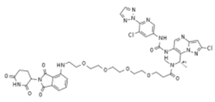
A



Peptidomimetic Approach

- Compound 3 is a substratemimetic peptidic covalent irreversible inhibitor of MALT1
- Compound 3 suppresses the growth of ABC DLBCL tumors in vivo

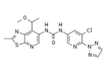
B



Peptidomimetic Approach

- Lead compound JH-XI-26 recruits an E3 ubiquitin ligase to target MALT1 for degradation
- JH-XI-26 decreases MALT1 levels and inhibits MALT1 scaffolding activity

C

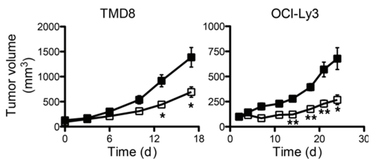


Allosteric Approach

- DS-01-121-02 and JH-XII-135 are 2 series of allosteric inhibitors (quinolines and thiazolopyridines)
- Significant effects on a PD marker of MALT1 inhibition upon oral dosing in mice

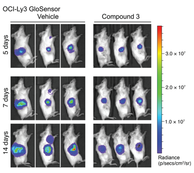
Inhibition of ABC DLBCL tumor growth in vivo

D



- Tumor growth curve for xenografts of the ABC DLBCL cell lines TMD8 (from NOD-SCID mice; n = 9/group) and OCI-Ly3 (from NSG mice; n = 10/group) following compound 3 treatment.
- Mice were treated with 30 mg/kg b.i.d. compound 3 or the same dose of vehicle for 16 or 24 consecutive days, respectively.

E



- Bioluminescence signal intensity quantification.
- Data represent the mean ± SEM. *P ≤ 0.05, **P ≤ 0.01, ***P< 0.001, and P = 0.02, by unpaired, 2-tailed Student's t test.

IP Status & Publication(s)

Intellectual Property

Patent Number	Patent Family
US 9592223 B2 (2017.03.14)	PCT, KR, US, EP, JP, CN, CA, AU
US 10711036 B2 (2020.07.14)	PCT, US, EP, JP
US 10689366 B2 (2020.06.23)	PCT, US, EP, JP
US 11248007 B2 (2022.02.15)	PCT, US, EP, JP

Publication(s)

- Hatcher at al. (2019) Peptide-based covalent inhibitors of MALT1 paracaspase. Bioorganic & Medicinal Chemistry Letters
- Scott at al. (2019) Quinoline and thiazolopyridine allosteric inhibitors of MALT1. Bioorganic & Medicinal Chemistry Letters
- Fontan at al. (2018) Specific covalent inhibition of MALT1 paracaspase suppresses B cell lymphoma growth. Journal of Clinical Investigation