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Inhibitors of MALT1 for the Treatment of Lymphomas

Lead Inventor:

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Developed in collaboration with Dana Farber Cancer Institute and Boston Children's Hospital

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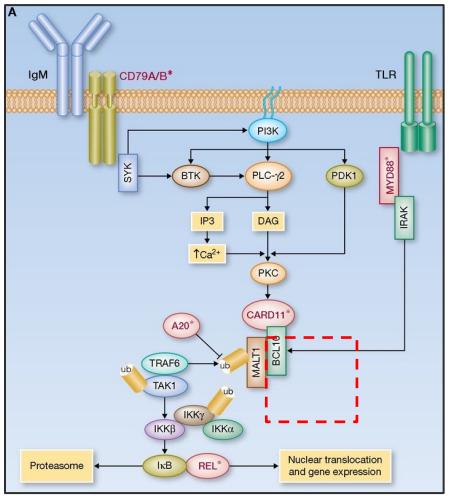
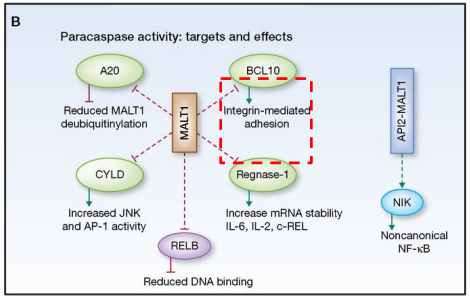
MALT1 is a mediator of NF-κB signaling and a promising therapeutic target for B-cell lymphomas

MALT1: Target Overview





- 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

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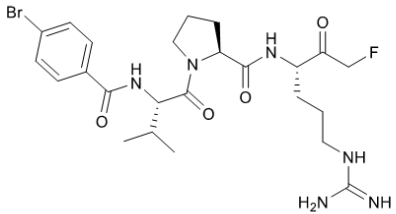
Fontan. J Clin Inv. 2018. Fontan. Clin Can Res. 2013.

WCM researchers have developed three promising approaches for therapeutic MALT1 inhibition

Weill Cornell Medicine MALT1 Inhibitor Programs

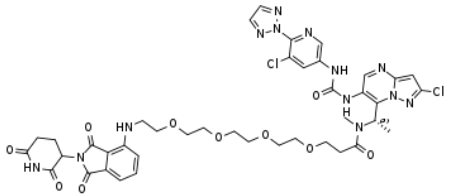
Peptidomimetic Approach

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



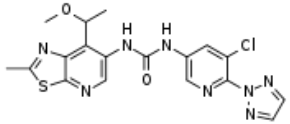
PROTAC Approach

- 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



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



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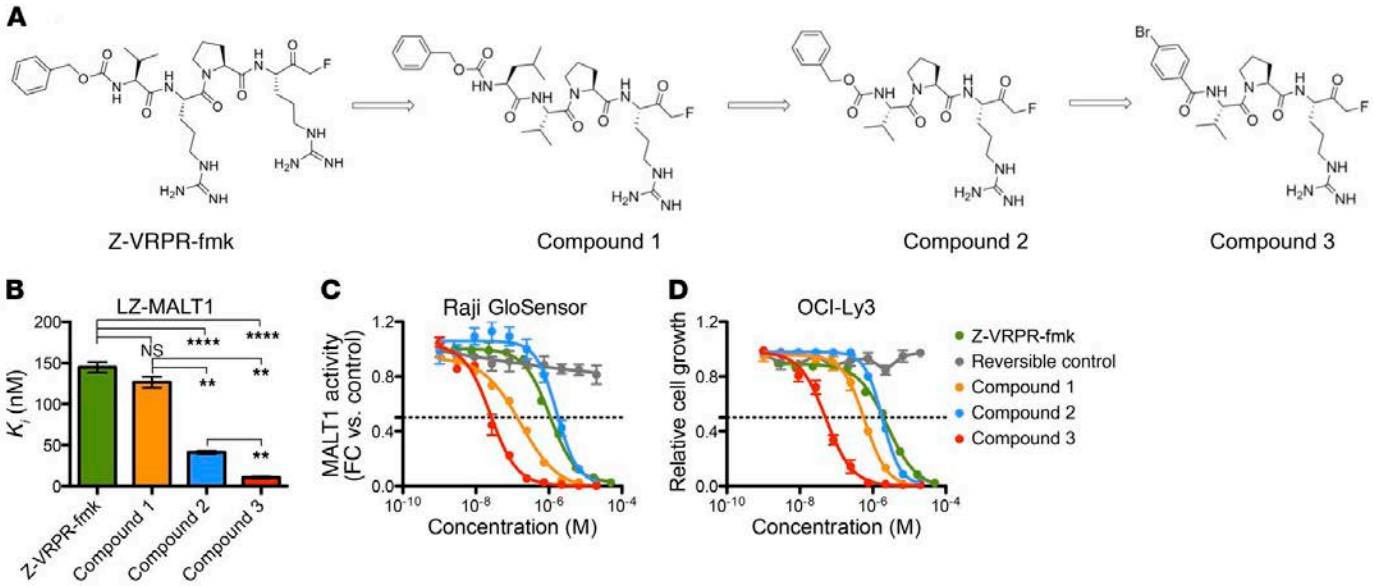
Compound 3 is a potent substrate-mimetic peptidic irreversible inhibitor of MALT1 protease activity

MALT1 Inhibition: Peptidometic Approach



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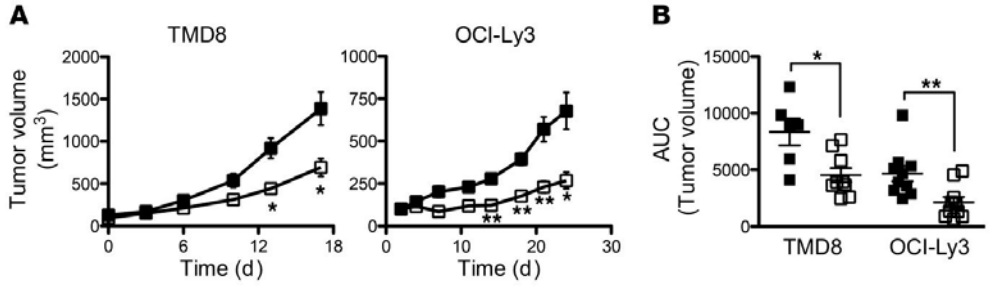
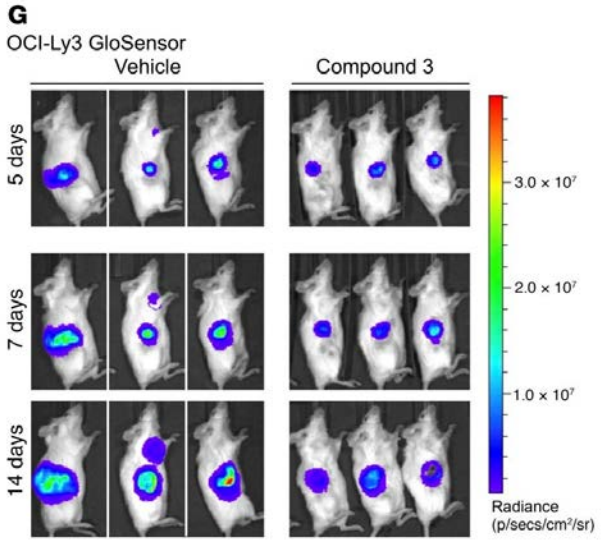
Fontan. J Clin Invest. 2018.

Compound 3 suppresses the growth of ABC DLBCL tumors in vivo

MALT1 Inhibition: Peptidometic Approach





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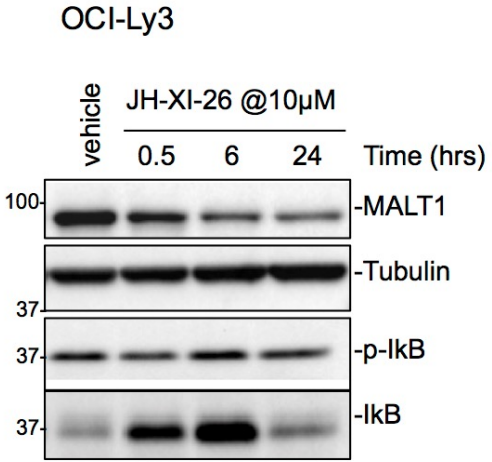
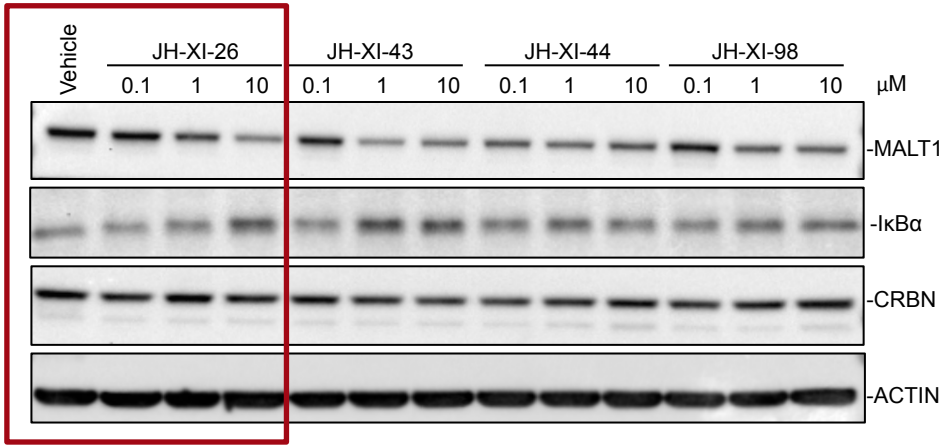
Fontan. J Clin Invest. 2018.

Proteolysis Targeting Chimeras (PROTAC): bifunctional compounds that inhibit MALT1 and promote degradation

MALT1 Inhibition: PROTAC Approach

- Treatment of OCI-Ly3 cells with JH-XI-26 results in a decrease in MALT1 levels, and increase of IκBα (an NF-κB inhibitor protein) levels





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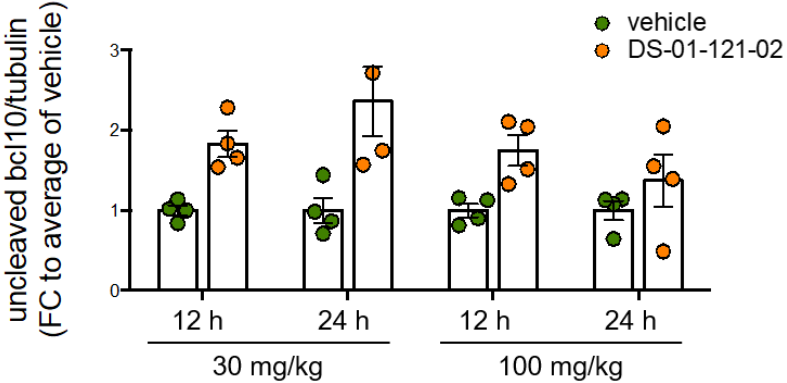
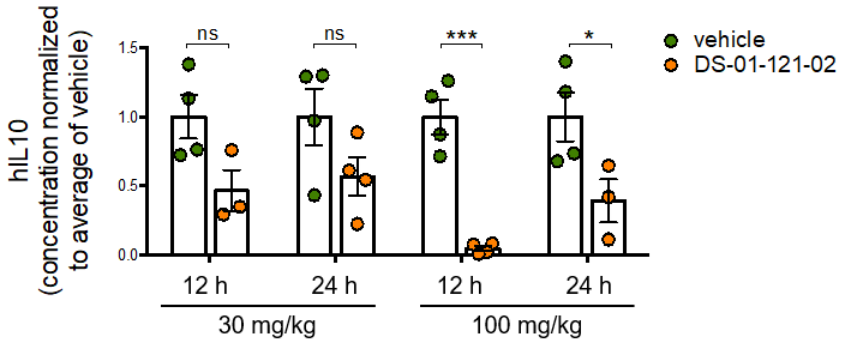
US Patent 10,689,366.

DS-01-121-02 is a quinoline allosteric MALT1 inhibitor with good cell potency and excellent target class selectivity

MALT1 Inhibition: Allosteric Approach

- Compounds have excellent MALT1 inhibitory properties, specificity, and PK/PD
- DS-01-121-02 has been shown to inhibit the cleavage of BCL10 in tumors (left), while also decreasing levels of IL10 in plasma (right)





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Source Box.

There are currently only a few MALT1 inhibitors in active commercial development

MALT1 Pipeline Overview

Candidate	Company	Type	Stage	Lead Indication
JNJ-67856633	janssen	MALT1 Inhibitor (Small Molecule)	Phase 1	Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia
MPT-0118	MonopTeros	MALT1 Inhibitor (Small Molecule)	Phase 1/1b	Advanced or Metastatic Refractory Solid Tumors
CTX-177	Chordia Therapeutics; ONO PHARMACEUTICAL CO.,LTD.	MALT1 Inhibitor (Small Molecule)	Preclinical	Non-Hodgkin Lymphoma

Significant competitive headroom exists for additional MALT1 inhibitor programs targeting heme and solid tumors

The MALT1 program is supported by a robust IP portfolio and multiple peer-reviewed articles

IP Status and Publications

- **Intellectual Property:**
  - US Patent 9,592,223 and EP Patent 2,916,656: “Small molecule inhibitors of MALT1.”
  - US Patent 10,689,366 and JP Patent 7,097,880: “Compounds for MALT1 degradation.” (Issued Jun 23, 2020)
  - US Patent 10,711,036: “MALT1 inhibitors and uses thereof.” (Issued Jul 14, 2020). Additional issued patents in FR, DE, IE, GB
  - US Patent 11,248,007 and JP Patent 7,142,022: “Inhibitors of MALT1 and uses thereof.” (Issued Feb 15, 2022))
  - Additional related filings in EP
  - Cornell Dockets: D-5946, D-7251, D-7556, D-7602
- **Publications:**
  - Xia et al. BCL10 mutations define distinct dependencies guiding precision therapy for DLBCL. *Cancer* Discov. 2022
  - Fontan et al. “Identification of MALT1 feedback mechanisms enables rational design of potent antilymphoma regimens for ABC-DLBCL.” *Blood.* 2021.
  - Hatcher et al. “Peptide-based covalent inhibitors of MALT1 paracaspase.” *Bioorg Med Chem Lett.* 2019.
  - Scott et al. “Quinoline and thiazolopyridine allosteric inhibitors of MALT1.” *Bioorg Med Chem Lett.* 2019.
  - Fontan et al. “Specific covalent inhibition of MALT1 paracaspase suppresses B cell lymphoma growth.” *J Clin Invest.* 2018.

Lead WCM Inventor: Ari M. Melnick

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M.D., University of Buenos Aires, 1990

Research interests: Understanding the mechanisms through which transcriptional and epigenetic regulation occur during normal differentiation and how these processes become disrupted in human leukemias and lymphomas.

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