2021 ASH Annual Meeting & Exposition

Characterization of Potent Paracaspase MALT1 Inhibitors for Hematological Malignancies

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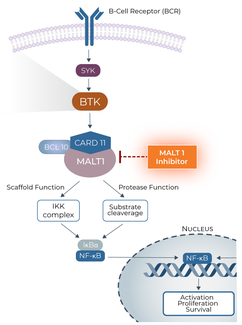
Introduction

- MALT1 is considered a potential therapeutic target for several subtypes of non-Hodgkin B-cell lymphomas and chronic lymphocytic leukemia (CLL).
- Previously, we described the discovery of novel and potent MALT1 inhibitors with anti-proliferative effects in non-Hodgkin B-cell lymphoma cells.
- Here, we highlight the strong anti-tumor activity of our MALT1 inhibitors across multiple tumor models including patient derived models, and the combination potential with other agents including standards-of-care.

MALT1 Is a Paracaspase Involved in NF-kB Signaling



Adapted from *Cell. Mol. Life Sci.* (2016) 73:459–473.

- MALT1 is one of the key regulators of physiological antigen receptor signalling in B cells and T cells, also the only component of the CARMA1-BCL10-MALT1 (CBM) signalosome which has proteolytic activity.
- Following antigen-receptor stimulation and the activation of CBM complex, MALT1 triggers NF-kB signaling and lymphocyte activation. MALT1 targets key proteins in a negative feedback loop mediating termination of the NF-κB response: a) as a scaffolding protein to activate the Inhibitor of IκB Kinase (IKK) complex and b) as a protease to inactivate negative regulators such as RelB and A20.
- Constitutive activation of the NF-κB signaling pathway is a molecular hallmark of activated B cell like diffuse large B cell lymphoma (ABC-DLBCL), and mutations that trigger constitutive MALT1 protease activity (such as on CD79 and CARD11) cause malignant B cell signaling.

Methods

In vitro potency

Potency of Schrodinger's MALT1 inhibitors was measured in enzymatic assays. For the *in vitro* target engagement assays in OCI-LY3 and OCI-LY10 cells, cells were treated with increasing concentrations of MALT1 inhibitors for 24 hrs, following by measurement of uncleaved BCL10 in cell lysates using MSD assays (Mesoscale Discovery). For cell proliferation assays in OCI-LY3 and OCI-LY10 cells, cells were treated with increasing concentrations of MALT1 inhibitors for 96 hrs, followed by CellTiter-Glo assay (Promega) to measure cell viability.

In vivo efficacy

LY2298 model: Fresh tumor tissues from mice bearing established primary human lymphoma cancer tissues were harvested and the tumor fragments were inoculated subcutaneously at the right front flank region into female NOD/SCID mice (GemPharmatech Co., Ltd) for tumor development. The randomization started when the mean tumor size reached approximately 148 mm^3.

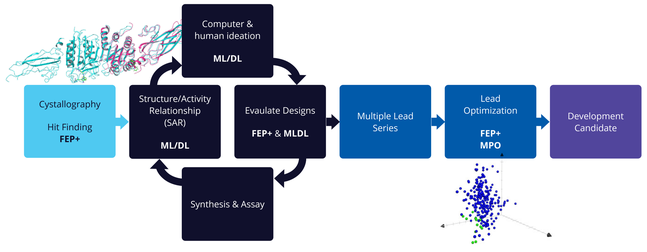
OCI-LY10 model: CB17 SCID mice (Beijing HFK bio-science CO.,Ltd) were inoculated subcutaneously on the right flank with OCI-LY10 tumor cells (1×10^7) in 0.1 mL of IMDM Medium and High Concentration Matrigel mixture (1:1 ratio) for model development. The randomization started when the mean tumor size reached approximately 184 mm^3. OCI-LY3 Model: NCG mice (GemPharmatech Co., Ltd) were inoculated subcutaneously on the right flank with $1 \times 10^{\wedge 7}$ OCI-LY3 tumor cells in 0.1 mL of RPMI-1640 and Matrigel mixture (1:1 ratio) for model development. The treatments for the study were started when the mean tumor volume reached about 158 mm^3.

REC-1 Model: NOD/SCID mice (GemPharmatech Co., Ltd) inoculated subcutaneously on the right flank with REC-1 tumor cells ($1 \times 10^{\wedge 6}$) in 0.1 mL of 1:1 RPMI-1640 and Matrigel mixture (1:1 ratio) for tumor development. The treatments for the study were started when the mean tumor volume reached about 173 mm^3.

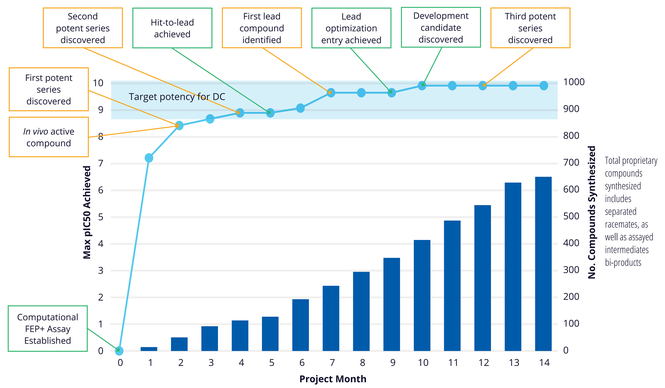
Tumor measurements and body weights were collected twice every week. Tumor volumes were measured twice per week after randomization in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: V = (L x W x W)/2, where V is tumor volume, L is tumor length (the longest tumor dimension) and W is tumor width (the longest tumor dimension perpendicular to L).

Discovery of Novel MALT1 Inhibitor Candidates in Under Two Years

- Schrödinger free energy perturbation technology (FEP+) enabled identification and advancement of multiple novel and promising series
  - Exploration of billions of human and computer designed compounds and FEP+ potency profiling of ~12,500 ideas allowed highly efficient chemistry execution of best hit series and best molecules.
  - Multi-parameter optimization (MPO) allow prioritization of ideas with both good potency and drug-like properties during lead optimization.



Potency Optimization Progress Using FEP+



Multiple Unique Chemical Series Demonstrated Similar Activities

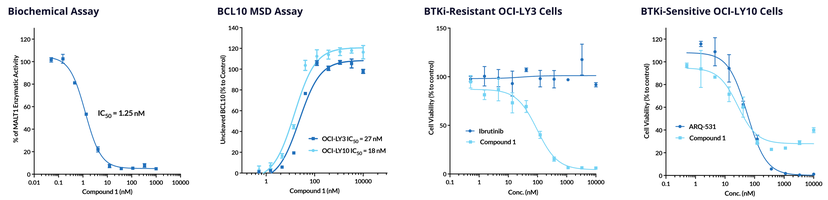
	Compound 1 (Series 1)	Compound 2 (Series 2)	Compound 3 (Series 3)
MALT1 IC_{50} (nM)	1.3	4.0	8.4
BCL-10 MSD (LY10) IC_{50} (nM)	21	51	69
Cell proliferation (LY10) IC_{50} (nM)	67	195	264

- Three unique series were identified with similar potency.
- Balanced but distinct ADME/PK profiles and broad intellectual property portfolio.
- We are well positioned with multiple opportunities to advance a best-in-class molecule.

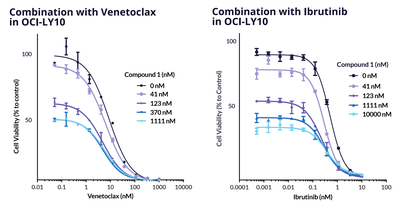
Conclusions

- We discovered novel, potent MALT1 protease small molecule inhibitors within multiple unique chemical series which offer distinct opportunities for lead and backup molecule selection.
- Schrodinger's MALT1 inhibitors are efficacious in *in vitro* B-cell lymphoma cell proliferation assays and in *in vivo* B-cell lymphoma xenograft models.
- These data suggest that targeting MALT1 may expand therapeutic options for patients with selected B-cell lymphomas, such as ABC-DLBCL, with the possibility of expanding into other B-cell lymphomas such as MCL.
- Furthermore, these small molecule MALT1 inhibitors demonstrate potential in combination with BTKi to overcome drug-induced resistance in patients with relapsed/refractory B-cell lymphomas.
- Taken together, the data present an opportunity to move a potential best-in-class MALT1 inhibitor into the clinic and strongly underscore the therapeutic potential of our MALT1 inhibitors. We are on-track to submit an IND for our MALT1 development candidate to the FDA in the first half of 2022.

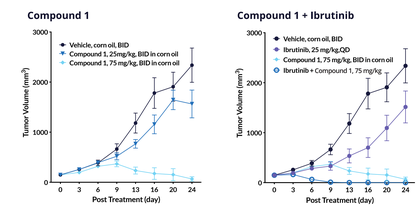
Compound 1, a Potent Novel MALT1 Allosteric Inhibitor, Shows Robust Target Engagement and Anti-proliferative Effects in ABC-DLBCL Cell Lines



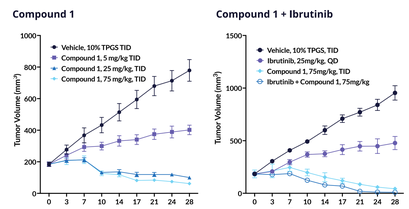
Strong Combination Effects with Venetocvlax or Ibrutinib in ABC-DLBCL Cell Lines



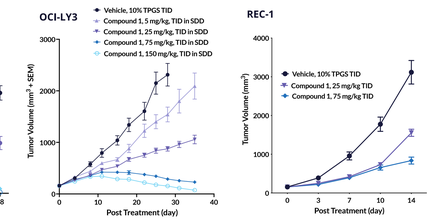
Strong Anti-Tumor Activities as a Single Agent and in Combination with Ibrutinib in ABC-DLBCL PDX Model LY2298



Strong Anti-Tumor Activities as a Single Agent and in Combination with Ibrutinib in ABC-DLBCL OCI-LY10 CDX Model



Strong Anti-Tumor Activities in ABC-DLBCL OCI-LY3 and MCL REC-1 CDX Models



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