Identification of Potent Paracaspase MALT1 Inhibitors for Hematological Malignancies

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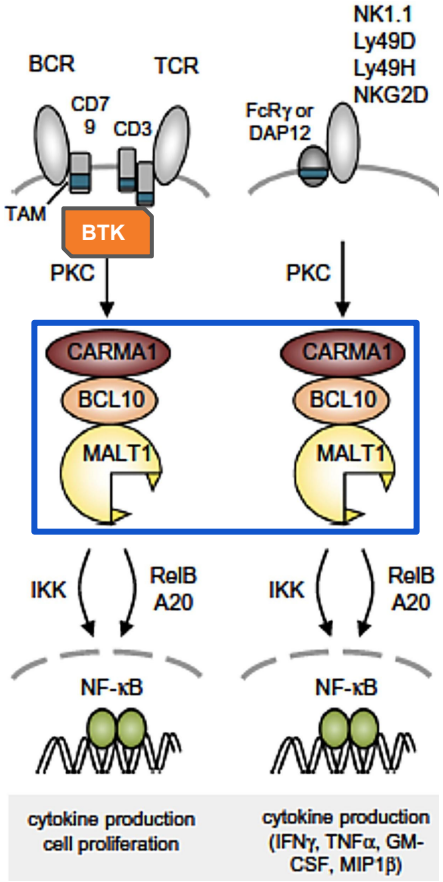
2. Triplet Therapeutics

Disclosure

All Schrödinger employees listed are stockholders of Schrödinger, Inc

MALT1 is a Paracaspase Involved in NF-KappaB Signaling



- 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-kappaB 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

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

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
- Development candidate is on track to initiate IND-enabling studies in the first half of 2021

Crystallography

Hit Finding
FEP+

Computer & human ideation
ML/DL

Structure/Activity Relationship (SAR)
ML/DL

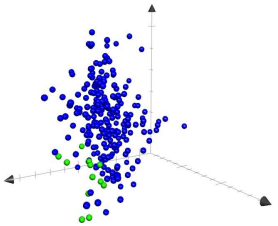
Synthesis & Assay

Evaluate Designs
FEP+ & ML/DL

Multiple Lead Series

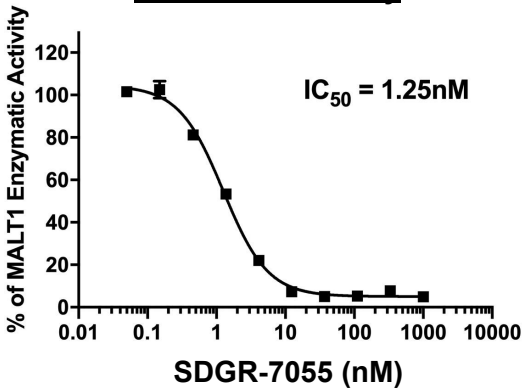
Lead Optimization
FEP+
MPO

Development Candidate

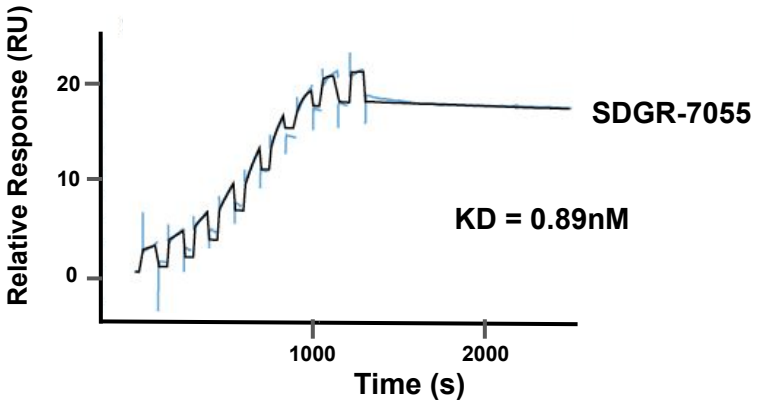


SDGR-7055, a Potent Novel MALT1 Allosteric Inhibitor, Drives Robust Target Engagement in ABC-DLBCL Cell Lines

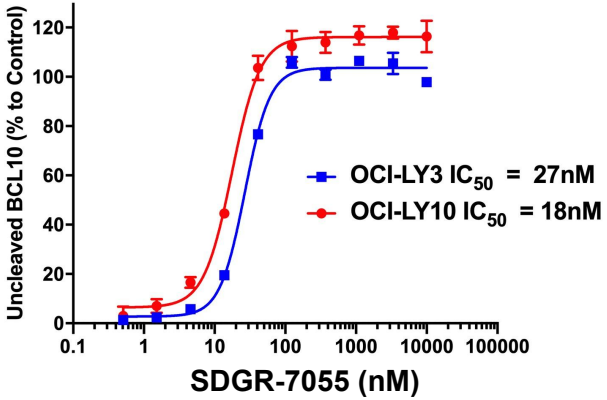
Biochemical Assay



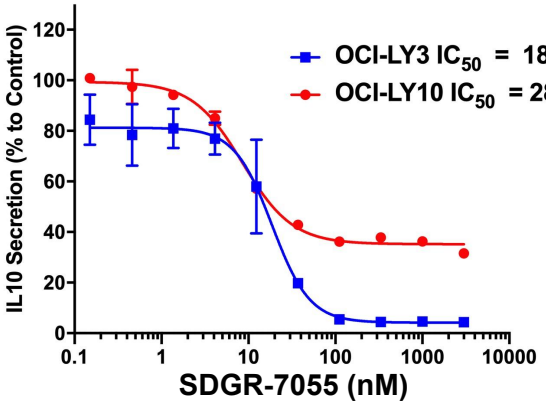
Surface Plasmon Resonance (SPR) Assay



BCL10 MSD Assay

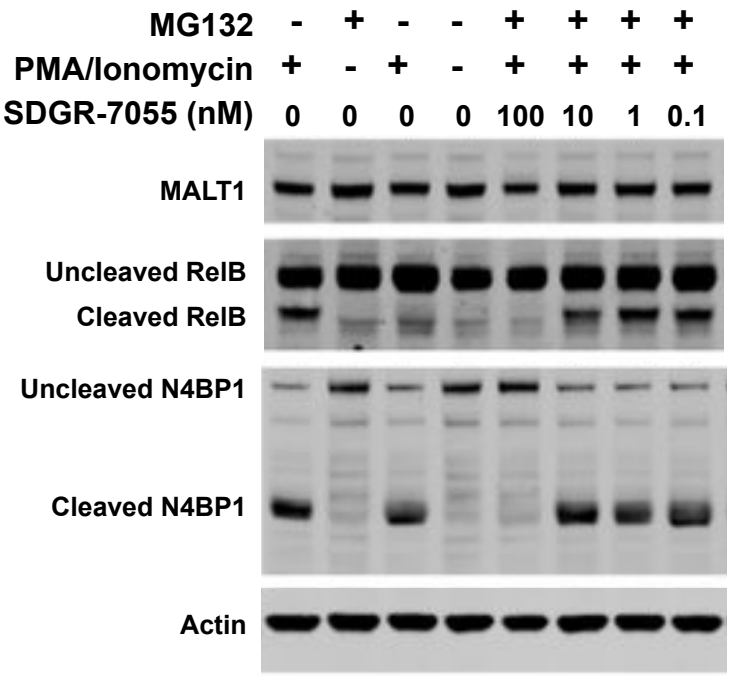


IL10 HTRF Assay

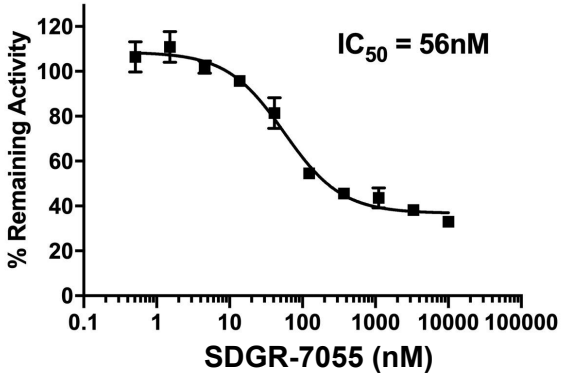


Our MALT1 Inhibitor Shows Strong Inhibitory Effects on Substrate Cleavage and NF-kB Transcriptional Activity

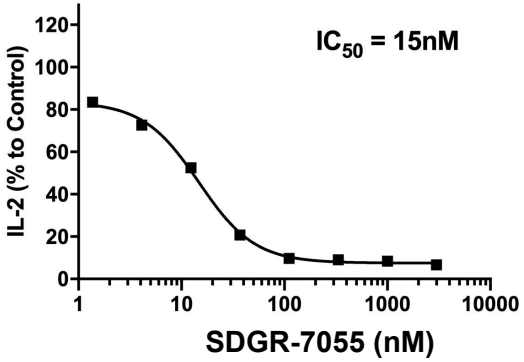
Western Blot on Cleavage of MALT1 Substrates RelB and N4BP1 in Jurkat cells



NFkB Reporter Assay in Jurkat Cells

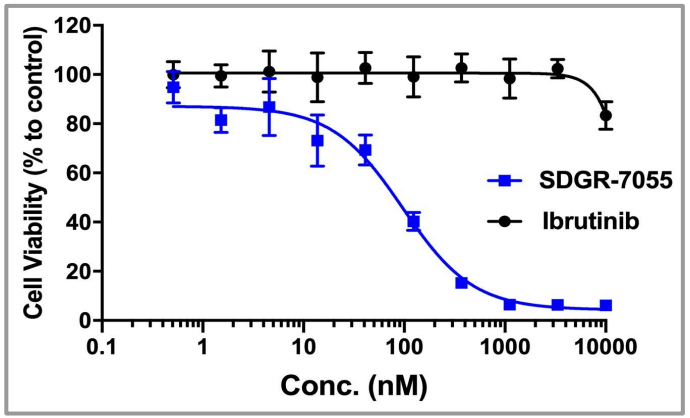


IL-2 Secretion in Jurkat Cells

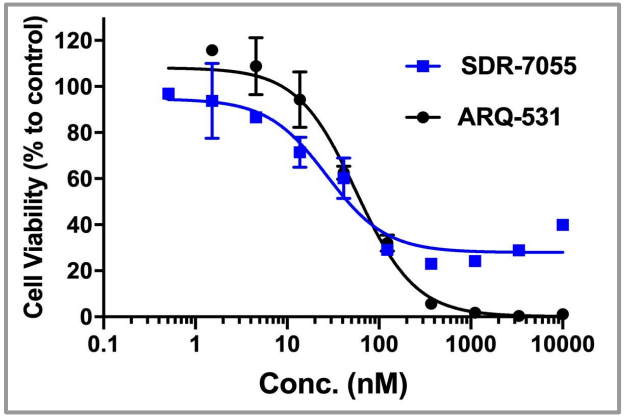


Strong Anti-Proliferative Effect as Single Agent and in Combination with venetoclax or ibrutinib in ABC-DLBCL Cell Lines

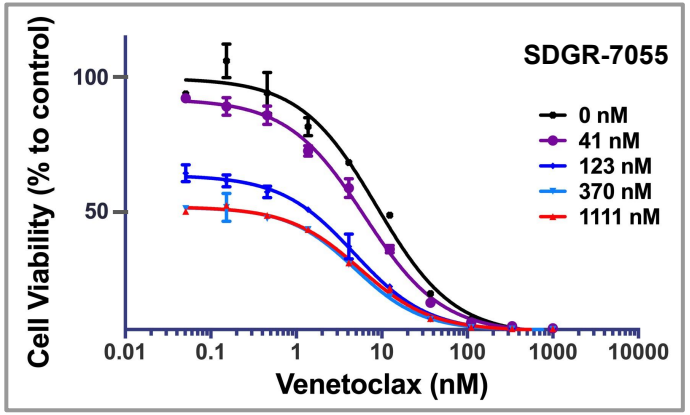
BTKi-Resistant OCI-LY3 Cells



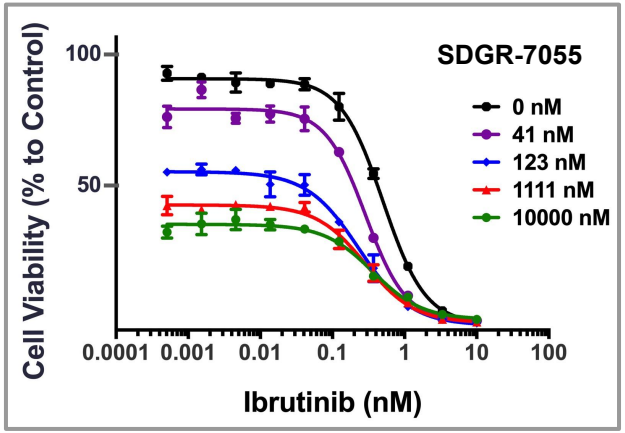
BTKi-Sensitive OCI-LY10 Cells



Combination with venetoclax in OCI-LY10



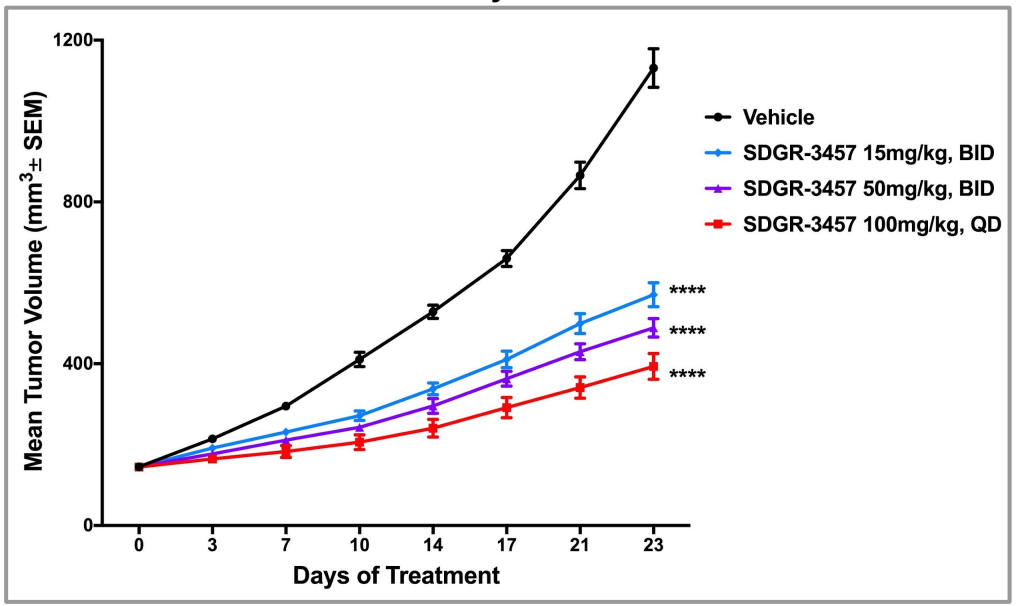
Combination with ibrutinib in OCI-LY10



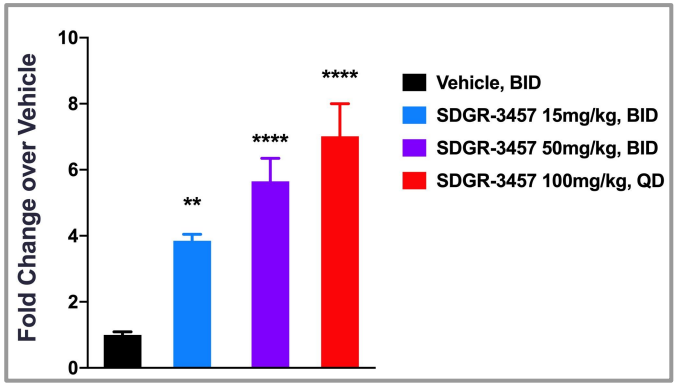
SDGR-3457 Demonstrated Strong Anti-tumor Growth Effect in OCI-LY3 Xenograft Model

Biochemical IC_{50} = 13nM

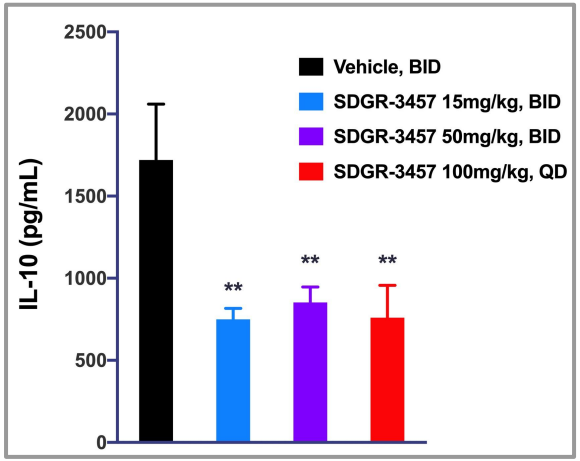
Anti-Tumor Activity in OCI-LY3 CDX



Tumor Uncleaved BCL10

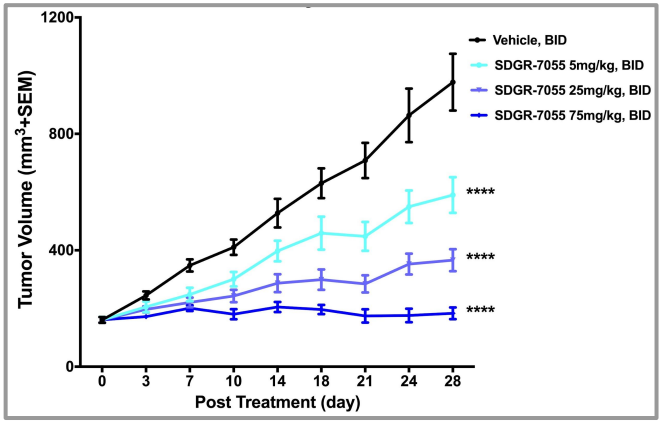


Plasma IL-10

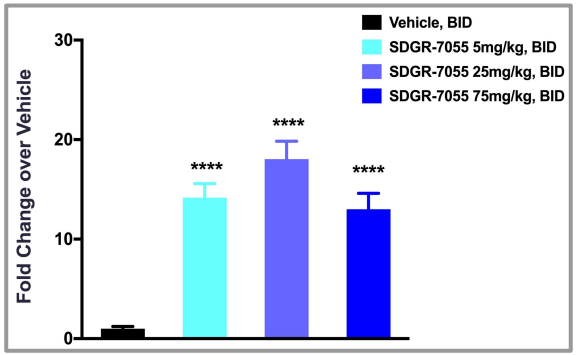


SDGR-7055 Demonstrated Strong Anti-tumor Growth Effects as Single Agent and in Combination with ibrutinib or venetoclax in OCI-LY10 Xenograft Model

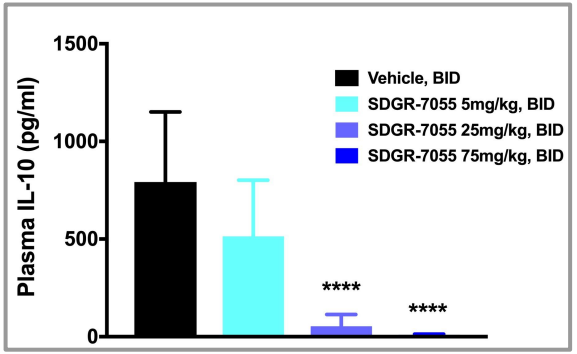
Anti-Tumor Activity in OCI-LY10 CDX



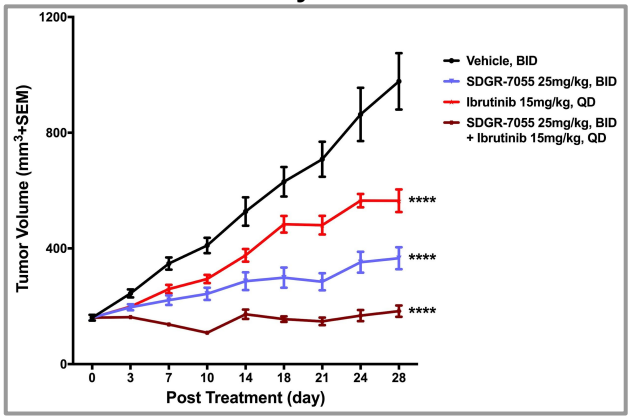
Tumor Uncleaved BCL10



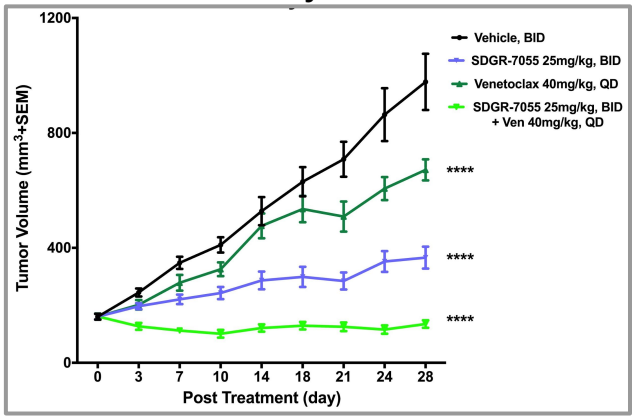
Plasma IL-10



Anti-Tumor Activity in OCI-LY10 CDX



Anti-Tumor Activity in OCI-LY10 CDX



Conclusions

- We have identified novel potent MALT1 small molecule inhibitors that are efficacious in the *in vitro* B-cell lymphoma cell proliferation assays and in the *in vivo* B-cell lymphoma xenograft models
- Dose-dependent tumor growth inhibition was observed in OCI-LY3 and OCI-LY10 xenograft models, with efficacy also observed in combination with venetoclax and combination with ibrutinib
- Our data suggest that targeting MALT1 may expand therapy options for patients with selected B-cell lymphomas, such as ABC-DLBCL
- 30-40% of DLBCL patients experience progression or relapse following R-CHOP treatment
- Our work provides insight into the anti-tumor efficacy of our inhibitors in B-cell lymphomas as single agent as well as potential combination with BTKi or venetoclax to overcome drug-induced resistance in patients with relapsed/refractory B-cell lymphoma
- IND-enabling efforts are scheduled to be initiated in the first half of 2021

Questions? Please email: wu.yin@schrodinger.com

Abstract

Results: We have identified novel small molecule MALT1 inhibitors using our proprietary physics-based Free Energy Perturbation (FEP+) modeling technology. Our compounds show potent (sub nM) inhibition of MALT1 enzymatic activity, as well as high binding affinity (sub nM) to MALT1 protein measured by Surface Plasmon Resonance (SPR). BCL10 is a binding partner of MALT1 that is cleaved by MALT1 at the C-terminus. Our inhibitors were efficacious in a target engagement assay showing prevention of BCL10 cleavage in Activated B-cell (ABC) subtype of diffuse large B cell lymphoma (DLBCL) cell lines OCI-LY3 and OCI-LY10, which are Bruton tyrosine kinase (BTK) inhibitor ibrutinib-resistant and -responsive respectively. Our compounds are potent inhibitors of IL10 secretion in both OCI-LY3 and OCI-LY10 cells, which is consistent with the inhibition of NF-κB signaling. We also examined the effect of our MALT1 inhibitors on ABC-DLBCL cell proliferation. Our inhibitors demonstrated potent anti-proliferative effects in both OCI-LY3 and OCI-LY10 cell lines, as well as synergistic effects with ibrutinib in a BTKi sensitive ABC-DLBCL cell panel. Examinations of a protease panel and off-target safety screening panel, as well as in vivo high dose tolerability study showed our compound had excellent selectivity and significant safety margin. Plasma IL10 and tumor BCL10 have been identified as robust PD markers in PK/PD studies in both OCI-LY3 and OCI-LY10 tumor bearing mice. Dose-dependent tumor growth inhibition was observed after 3 weeks of treatment in OCI-LY3 xenograft model, with efficacy also observed in combination with venetoclax.

Ongoing work: We are continuing to explore the synergistic effects of our compounds with BTK inhibitors in B-cell lymphoma mouse models. Preliminary data showed potent inhibition of IL-2 secretion in Jurkat cells from our compound treatment. Additional studies are ongoing to elucidate the role of MALT1 inhibition in Treg as well as Teffector cells in vitro and in vivo. Refinement of the current inhibitor series, using co-crystal structures, is in progress in preparation for further development of optimized molecules.

Conclusion and Future Plans: We have identified novel potent MALT1 protease small molecule inhibitors that are efficacious in the in vitro B-cell lymphoma cell proliferation assays and in the in vivo B-cell lymphoma xenograft model. Our data suggest that targeting MALT1 may expand therapy options for patients with selected B-cell lymphomas, such as ABC-DLBCL. Our work provided insight into the anti-tumor efficacy of our inhibitors in B-cell lymphomas as single agent, and ongoing work will continue to assess the potential combination with BTKi to overcome drug-induced resistance in patients with

Guidelines

Create a brief 5-minute PowerPoint presentation with accompanying audio narrating the contents of your poster and save your presentation as an MP4 file. A traditional poster layout PDF is not required and will not be accepted.

Your PowerPoint presentation should contain between 5- 8 slides, not including title and disclosure slide.

All presentations must include a disclosure slide.

Use of an ASH PowerPoint template is not mandatory. If you wish to use your own, please follow these guidelines.

16:9 aspect ratio

No commercial logos

Charts, drawings, and illustrations may be included as long as you have copyright permission to use them. Remember to keep illustrated and written material simple.

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As part of your poster presentation we will include your email address so that attendees can follow up with you on any questions related to your poster presentation.

Authors can include a QR code on their presentation if it links to additional information.