Discovery of the First MALT1 Allosteric Scaffolding Inhibitor

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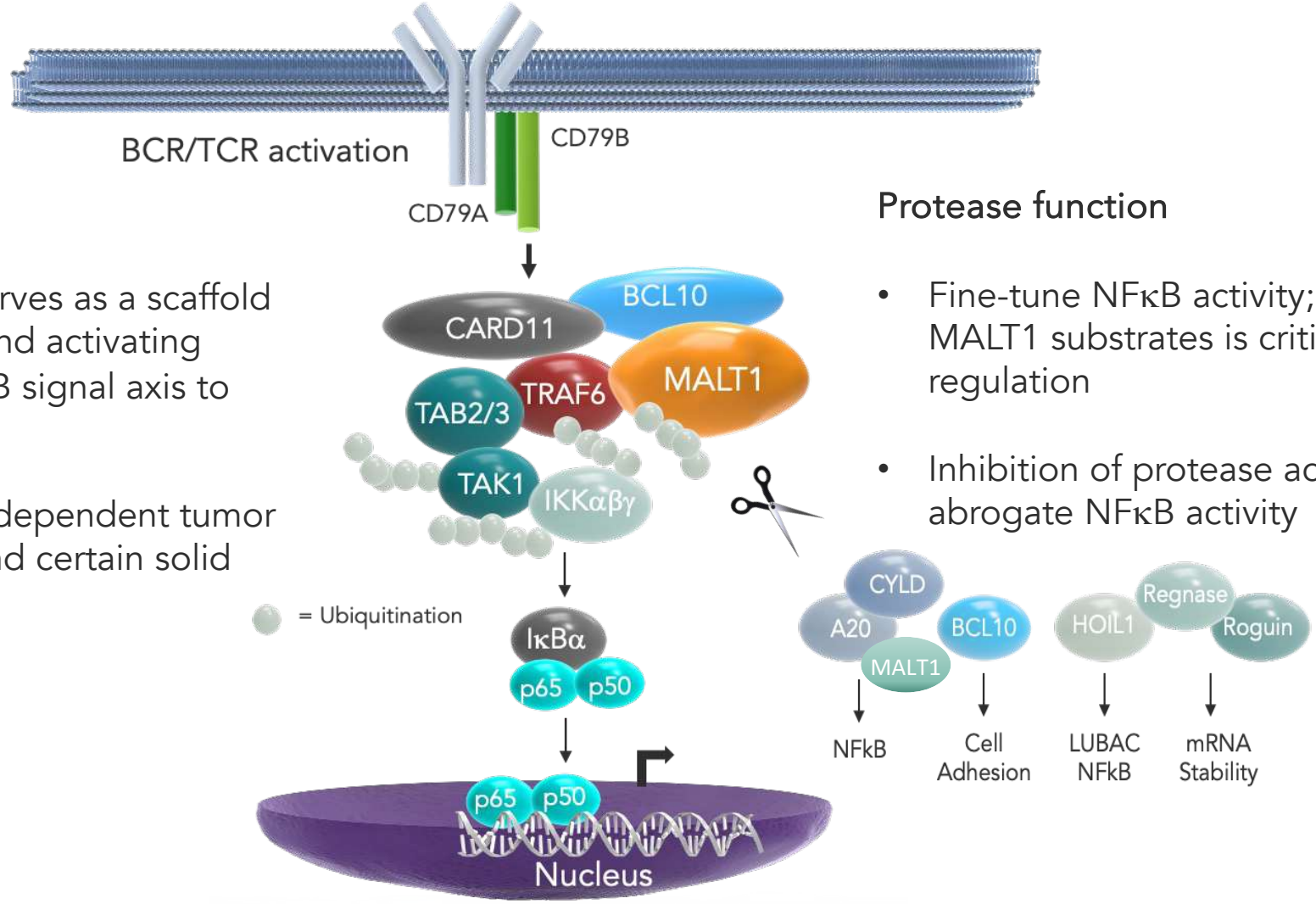
- HotSpot Therapeutics, Inc.

- 2023 American Society of Hematology Annual Meeting

Inhibition of MALT1 Scaffolding Activity Has Greater Impact on Canonical NFκB Signaling in Oncogenesis



Scaffolding function

- Activated MALT1 serves as a scaffold protein, recruiting and activating CBM/TRAF6/IKK/IκB signal axis to trigger NFκB signal
- **Essential** for NFκB-dependent tumor growth, e.g. NHL and certain solid tumors

Protease function

- Fine-tune NFκB activity; Cleavage of MALT1 substrates is critical for immune regulation
- Inhibition of protease activity **partially** abrogate NFκB activity

MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1

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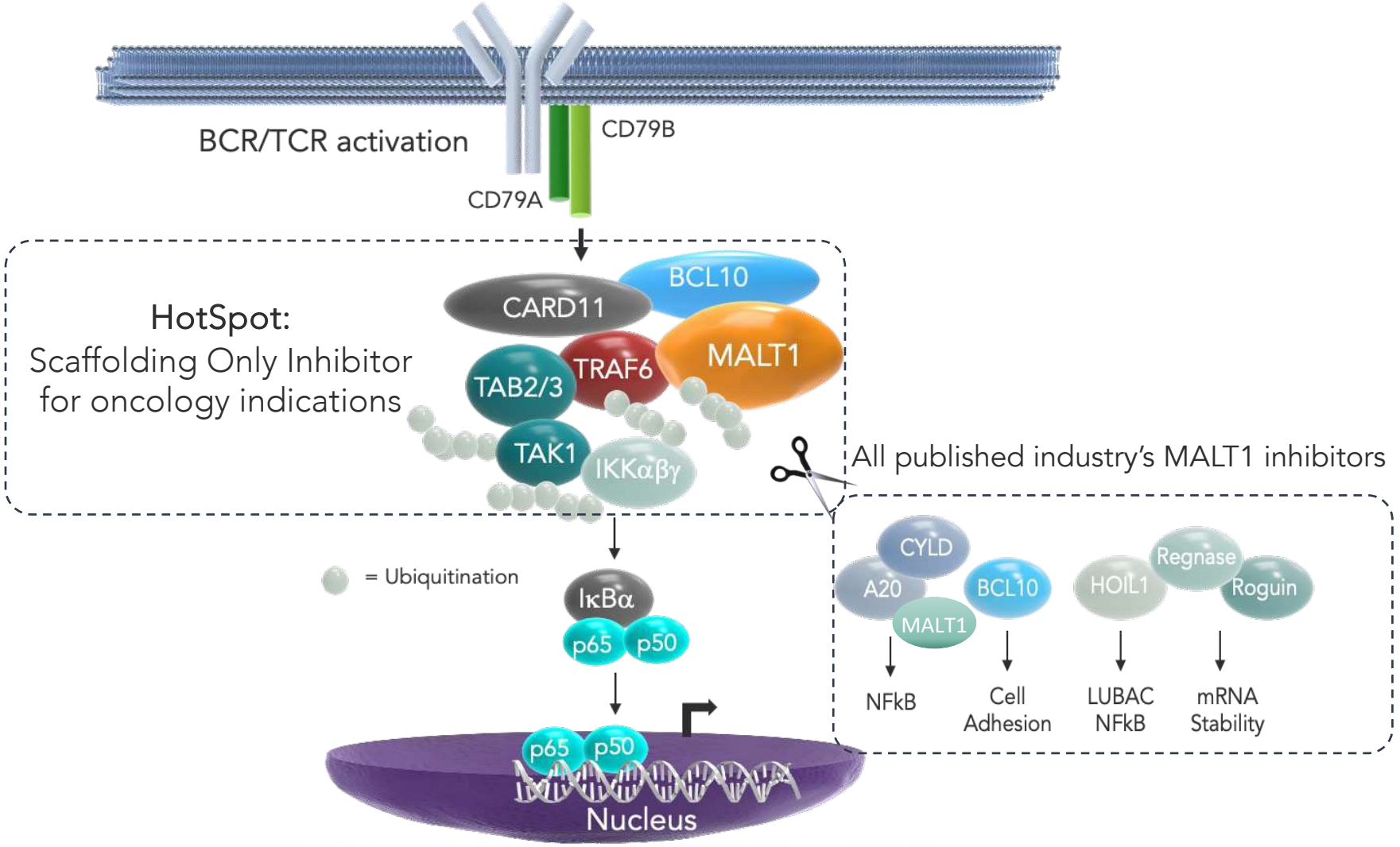
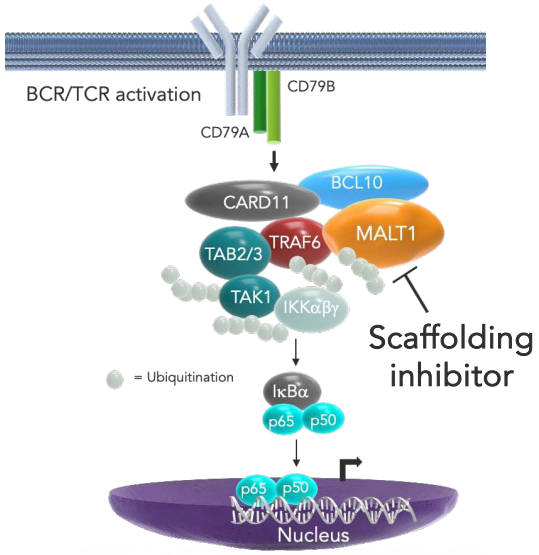
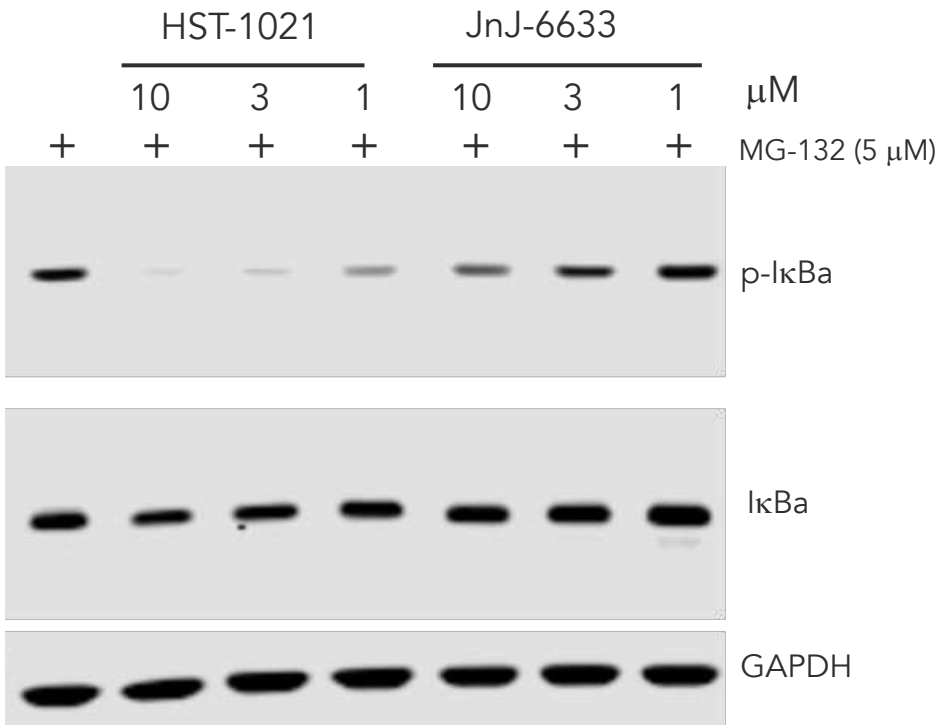


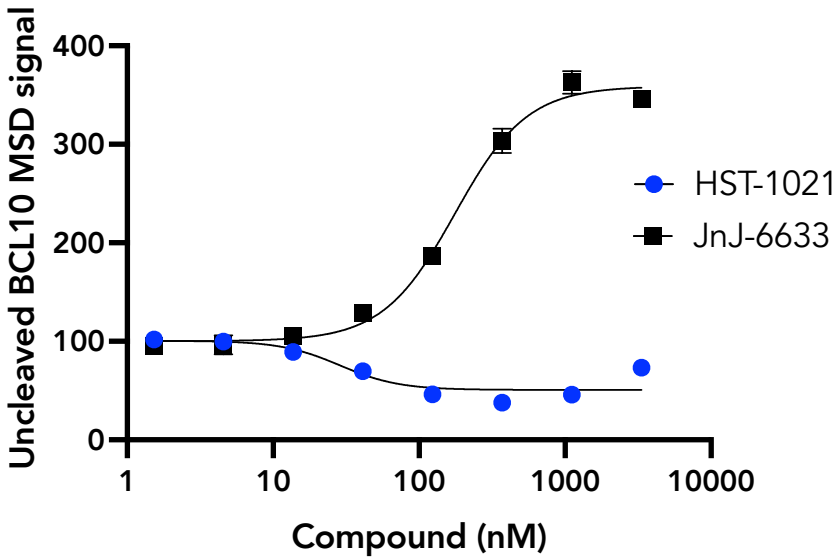
Smart Allostery™ Platform Discovered the First MALT1 Scaffolding Only Inhibitors



HST-1021 decreased pIκB level in OCI-Ly3



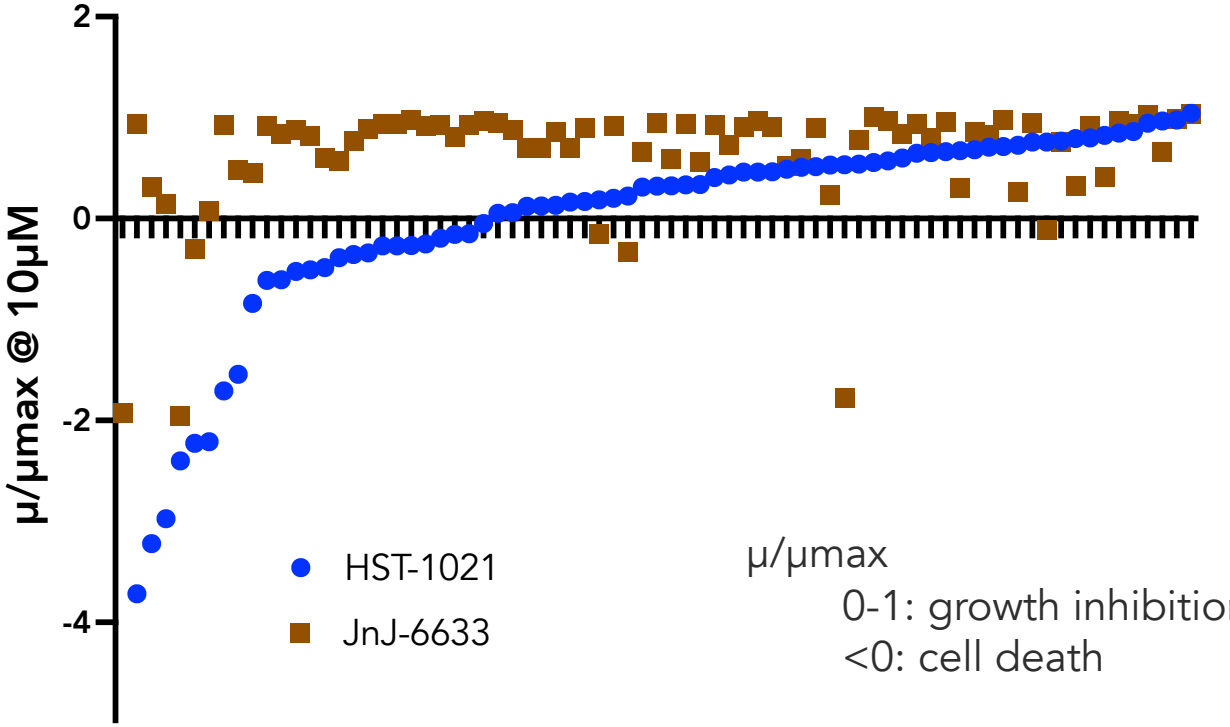
HST-1021 did not inhibit MALT1 cellular protease activity



HST-1021: MALT1 scaffolding inhibitor
JnJ-6633: competitor clinical investigational MALT1 protease inhibitor
MG-132: proteasome inhibitor
OCI-Ly3: B cell lymphoma cell line (CD79Bm, MYD88m, CARD11m)

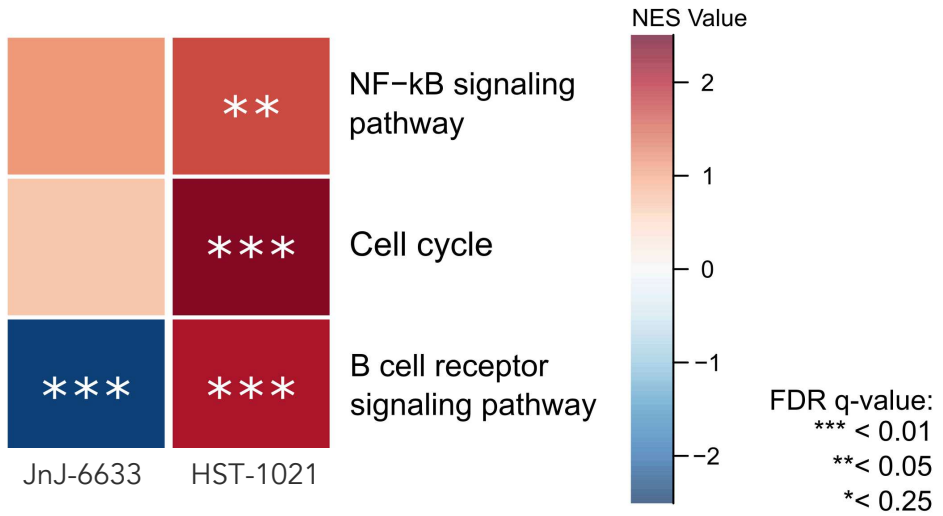
Broader and More Potent Activity of HST-1021 Than MALT1 Protease Inhibitor

In vitro lymphoma cancer cell panel proliferation screen (4-d)



μ/μmax
0-1: growth inhibition
<0: cell death

Cell lines with high NFκB and BCR activities are sensitive to MALT1 scaffolding inhibitor



- JnJ-6633: competitor clinical investigational MALT1 protease inhibitor

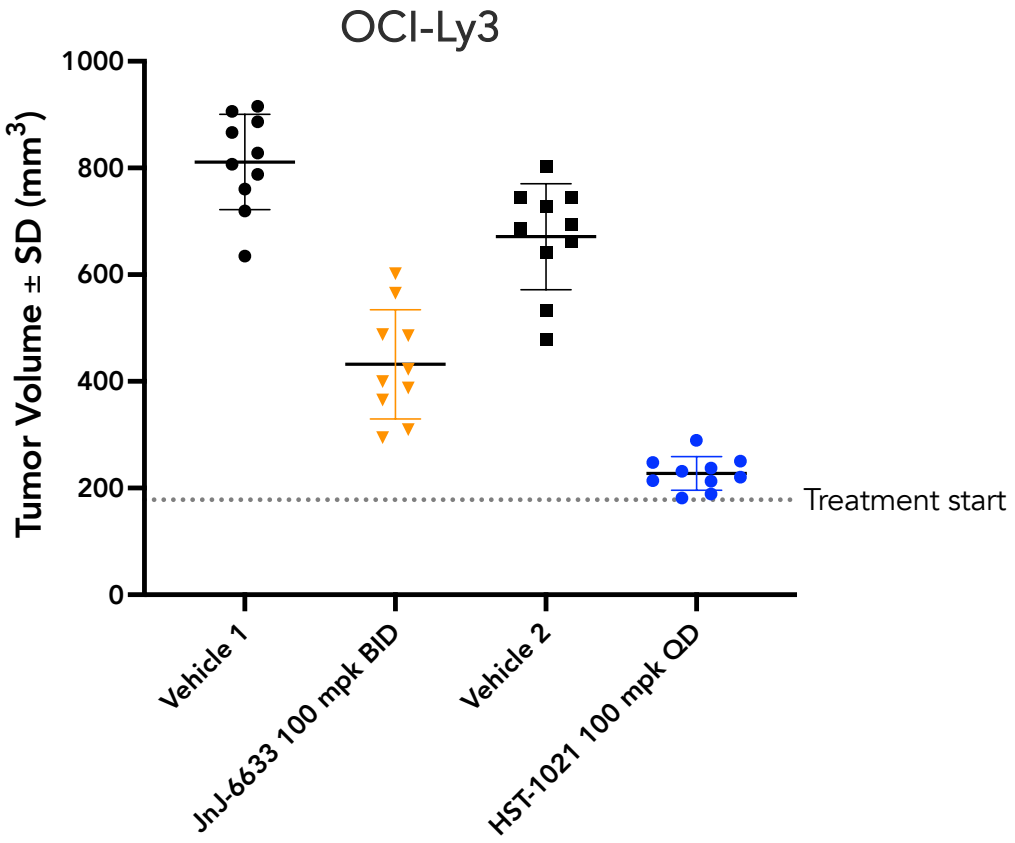
Scaffolding Inhibitor Demonstrated Potent and Broad Tumor Growth Inhibition

In vivo NFκB-driven DLBCL models		Scaffolding inhibitor	Protease inhibitor
		HST-1021	JnJ-6633
Protease sensitive DLBCL	OCI-Ly3: CD79B, MYD88, CARD11	Stasis-Regression (> 90% TGI)	Sensitive (60-80%)
	OCI-Ly10: CDK11B, PTEN, TP53, TP63, MYD88	Regression (>120% TGI)	Sensitive (60-80%)
NFκB-driven, protease insensitive DLBCL	TMD8: CD79A/B, MYD88, PIM1, IRF4, MYC, MALT1 constitutively active	Sensitive (>70%)	Insensitive (<30%)
	MC116: CARD11 and MALT1 copy number gain	Sensitive (>90%)	Insensitive (<20%)

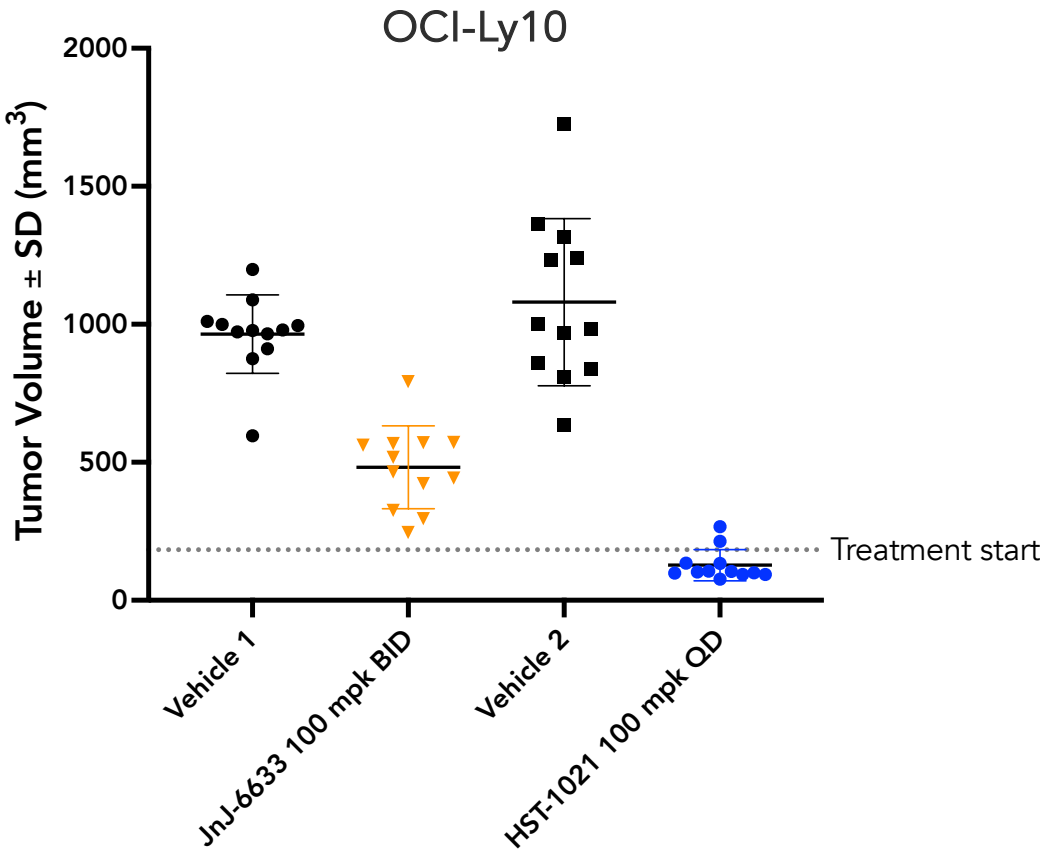
(%) = tumor growth inhibition

* JnJ-6633: competitor clinical investigational MALT1 protease inhibitor

Tumor Stasis or Regression Observed with Scaffolding Inhibitor in Protease Inhibitor Sensitive Models



OCI-Ly3 mutations: CD79B, MYD88, CARD11



OCI-Ly10 mutations: CDK11B, PTEN, TP53, MYD88

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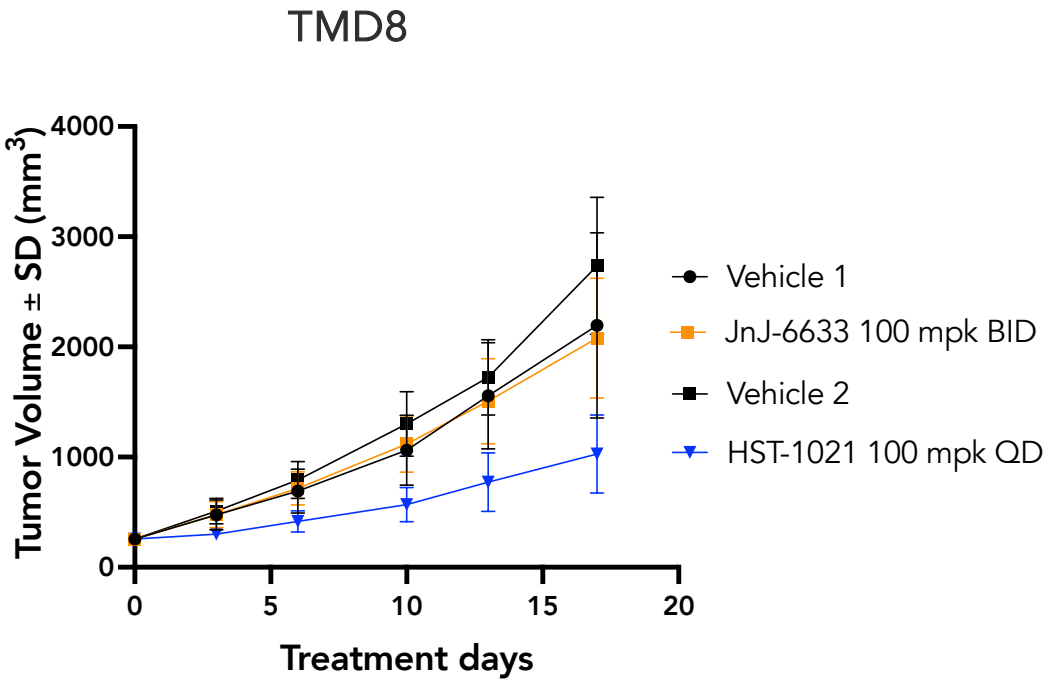
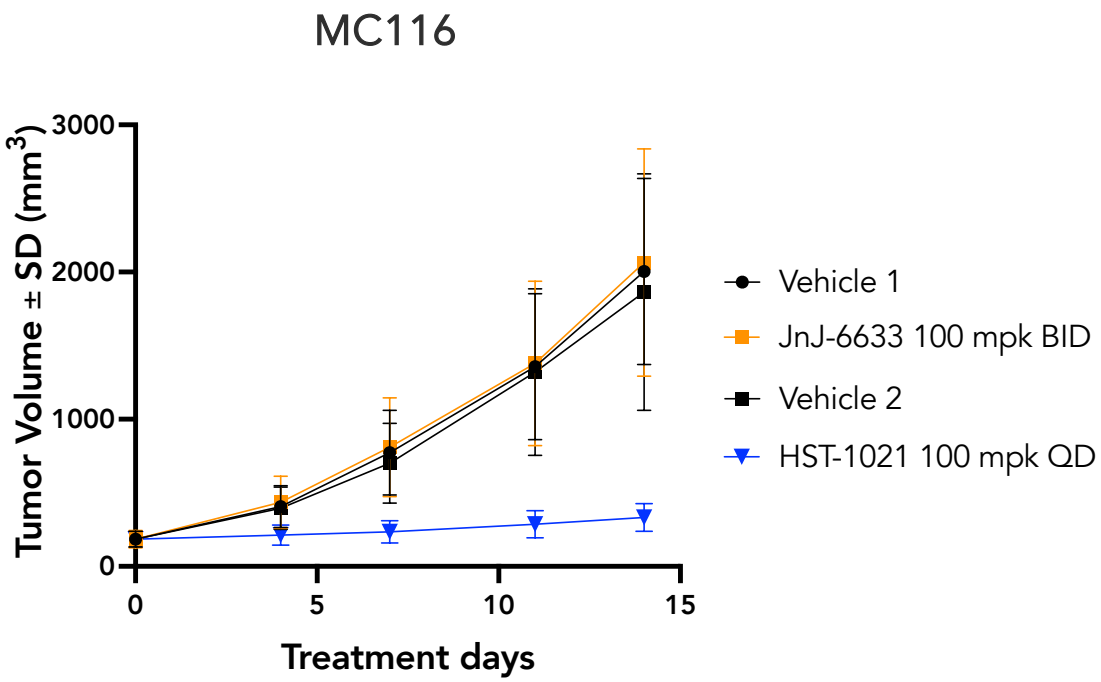
Tumor Growth Inhibition Observed With Scaffolding Inhibitor in NFκB-Dependent and Protease Inhibitor Insensitive Models



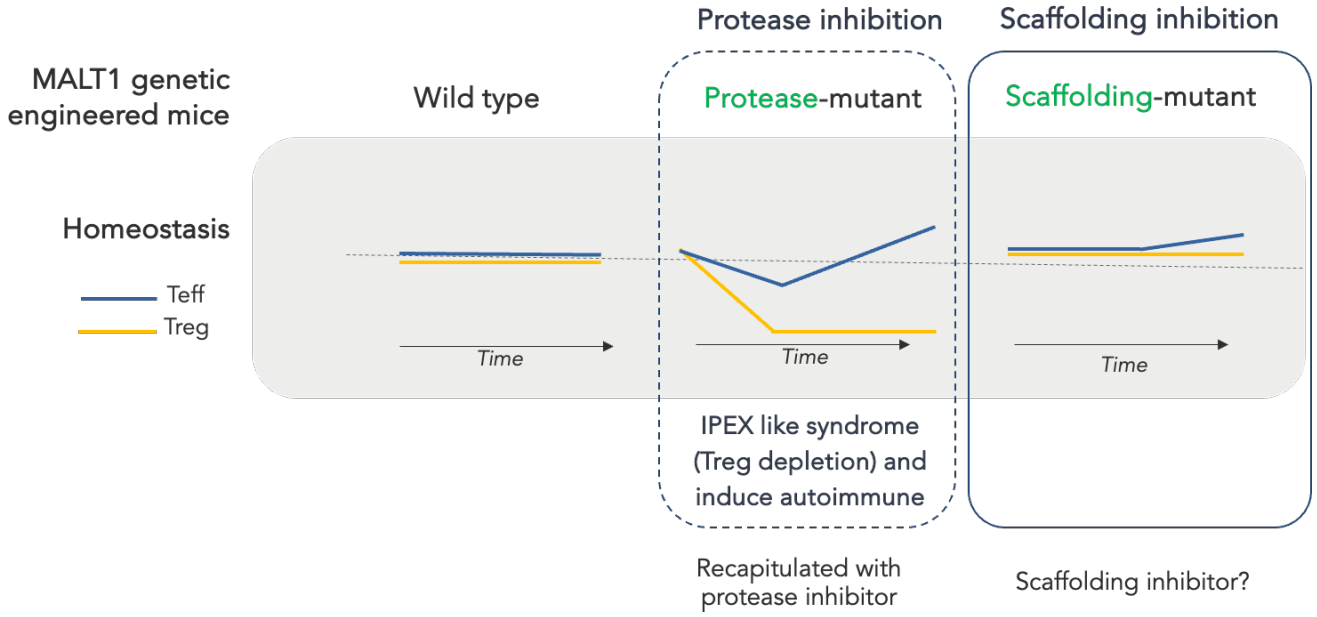


TMD8: CD79A/B, MYD88, PIM1, IRF4, MYC;
sensitive to BTK inhibitor

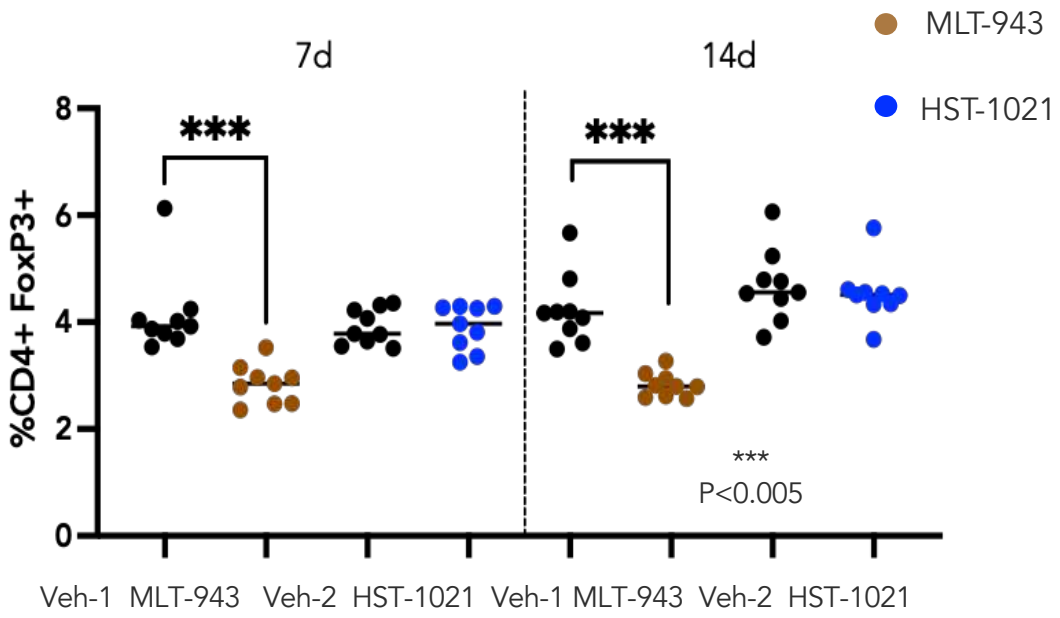
MC116: CARD11 and MALT1 copy number gain;
resistant to BTK inhibitor

* JnJ-6633: competitor clinical investigational MALT1 protease inhibitor

Scaffolding Inhibitor Is Differentiated From Protease Inhibitor by Avoiding Treg Depletion

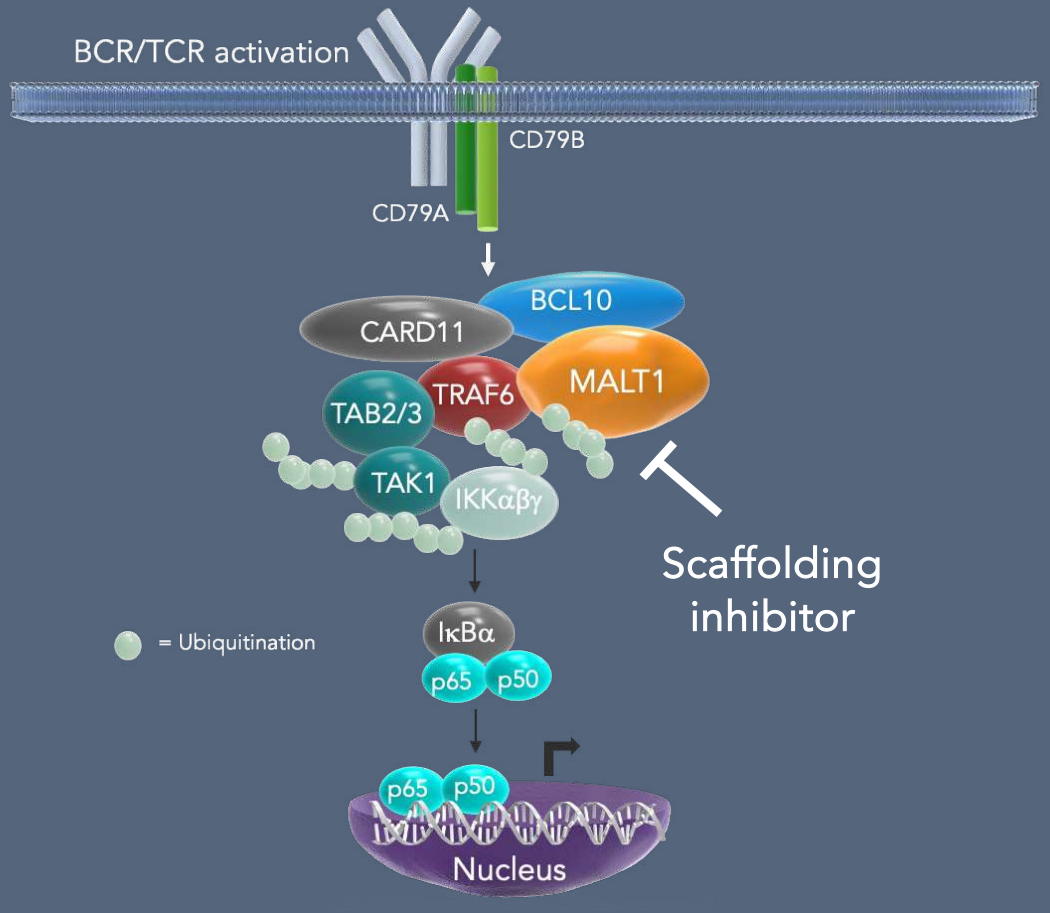


No Treg decrease observed in HST-1021 treatment group



MLT-943, a protease inhibitor

First-In-Class MALT1 Scaffolding Inhibitor



- First-in-class MALT1 scaffolding inhibitors discovered using Smart Allostery™ platform
- Scaffolding inhibitor is differentiated from protease inhibitors:
  - Potent and broad inhibition of NFκB-dependent tumor growth
  - Profound enhanced anti-tumor effects of HST-1021 in combination with BTKi or BCL2i
  - No Treg depletion
- IND filing with HST-1021 expected in 2024