Weill Cornell Medicine

Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

Lead Inventors:

Ari Melnick, M.D.

Professor of Medicine, Medicine, Weill Cornell Medical College

Gebroe Family Professor of Hematology / Oncology, Medicine, Weill Cornell Medical College

Business Development Contact:

Brian Kelly

Director, Technology Licensing

(646) 962-7041

bjk44@cornell.edu

Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

Background & Unmet Need

- Diffuse large B-Cell Lymphoma (DLBCL) is the most common hematological malignancy
- DLBCL is classified into three subgroups, of which Activated B Cell-like (ABC) DLBCL is the most aggressive and has the poorest outcomes
- Constitutive activation of NF-kB signaling is a hallmark of ABC-DLBCL, which is largely mediated by B Cell Receptor (BCR) signaling
- BTK inhibitors have had a large impact on treatment of other lymphomas and act downstream of BCR, but show only modest effects in DLBCL
- There are several targets along the BCR signaling pathway, including within the CARD11—BCL10—MALT1 (CBM) complex which can be mutated and may mediate BTK resistance
- **Unmet Need:** Better understanding of somatic mutations in ABC DLBCL to guide precision treatment selection

Technology Overview

- **The Technology:** Use of BCL-10 as a biomarker to guide precision therapy for ABC DLBCL
- **The Discovery:** Genome sequencing revealed that mutations in BCL10 are most common in ABC-DLBCLs
- BCL10 is a part of the CBM complex, which activates NF-kB signaling downstream of BCR
- Biochemical, structural, and functional analysis demonstrated that BCL10 mutations fall into two distinct classes:
    - Missense mutations in the CARD domain
    - Truncating mutations in the C-terminal
- **PoC Data:** Both BCL10 mutants with truncating and with missense mutations demonstrate resistance to BTK inhibitors
- Mutants with BCL10 truncating mutations are hypersensitive to MALT1 inhibitors, whereas missense BCL10 mutants are not

Inventors:
Ari Melnick
Liron David
Hao Wu
Min Xia

Patents:
US Application Filed

Publications:
Xia et al. *Cancer Discov*. 2022.

Biz Dev Contact:
Brian Kelly
(646) 962-7041
bjk44@cornell.edu

Cornell Reference:
D-10374

Weill Cornell Medicine

ABC DLBCL: Activated B Cell-like Diffuse Large B-Cell Lymphoma
BCR: B Cell Receptor
CBM: CARD11—BCL10—MALT1
DLBCL: Diffuse Large B-Cell Lymphoma

Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

Technology Applications

- Biomarker to guide precision therapy for use of BTK and MALT1 inhibitors for ABC DLBCL
- Biomarker for patient selection in MALT1 inhibitor clinical trials

Technology Advantages

- Determines which patients may benefit from alternatives to BTK inhibitors
- Identifies patients which would be most likely to respond to MALT1 inhibitor therapy

Supporting Data / Figures

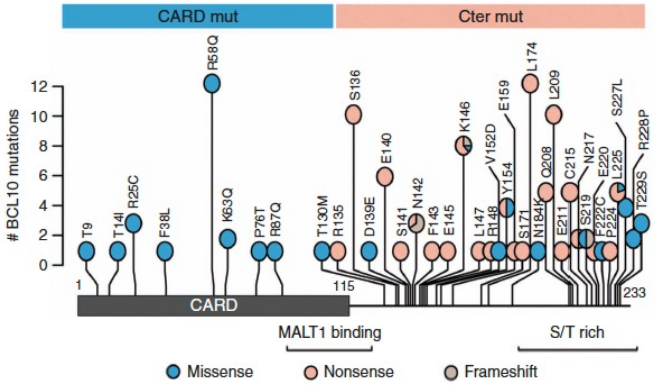

Figure 1: Two categories of BCL10 mutations in DLBCL were identified: Missense mutations in the CARD domain and truncating mutations in the C-terminal.

Inventors:
Ari Melnick
Liron David
Hao Wu
Min Xia

Patents:
US Application Filed

Publications:
Xia et al. *Cancer Discov*. 2022.

Biz Dev Contact:
Brian Kelly
(646) 962-7041
bjk44@cornell.edu

Cornell Reference:
D-10374

Weill Cornell Medicine

Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

Supporting Data / Figures

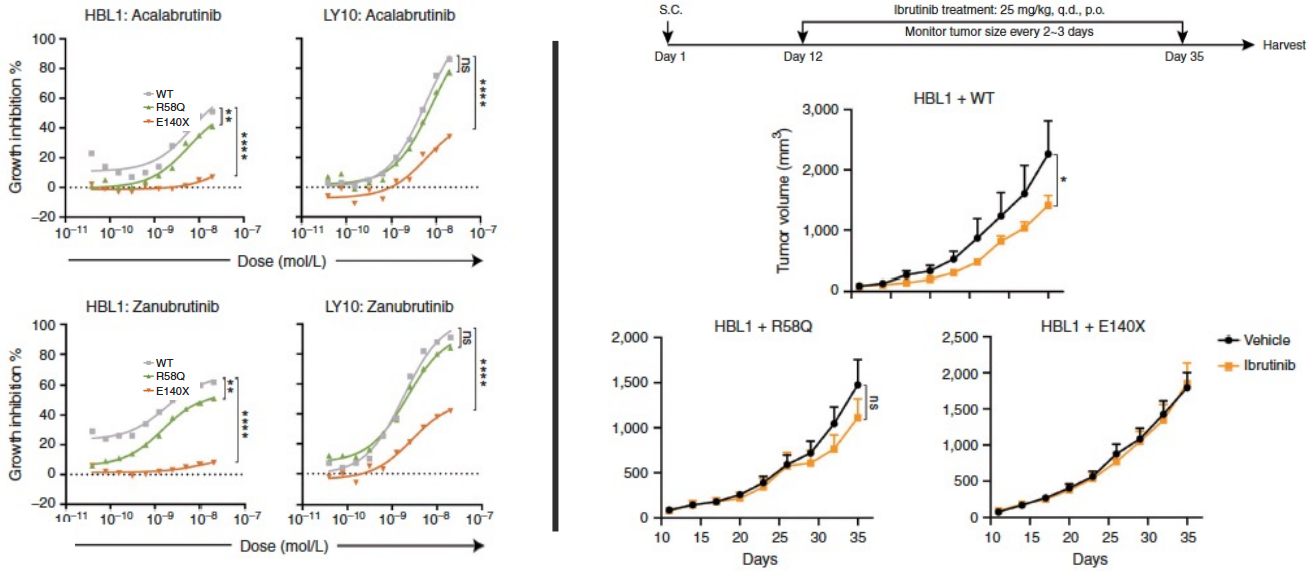

Figure 2: Both missense BCL10 mutants (R58Q) and truncated BCL10 mutants (E140X) demonstrated resistance to BTK inhibitor therapy in *in vitro* (**Left**) and *in vivo* PDX (**Right**) models.

Inventors:
Ari Melnick
Liron David
Hao Wu
Min Xia

Patents:
US Application Filed

Publications:
Xia et al. *Cancer Discov*. 2022.

Biz Dev Contact:
Brian Kelly
(646) 962-7041
bjk44@cornell.edu

Cornell Reference:
D-10374

Weill Cornell Medicine

Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

Supporting Data / Figures

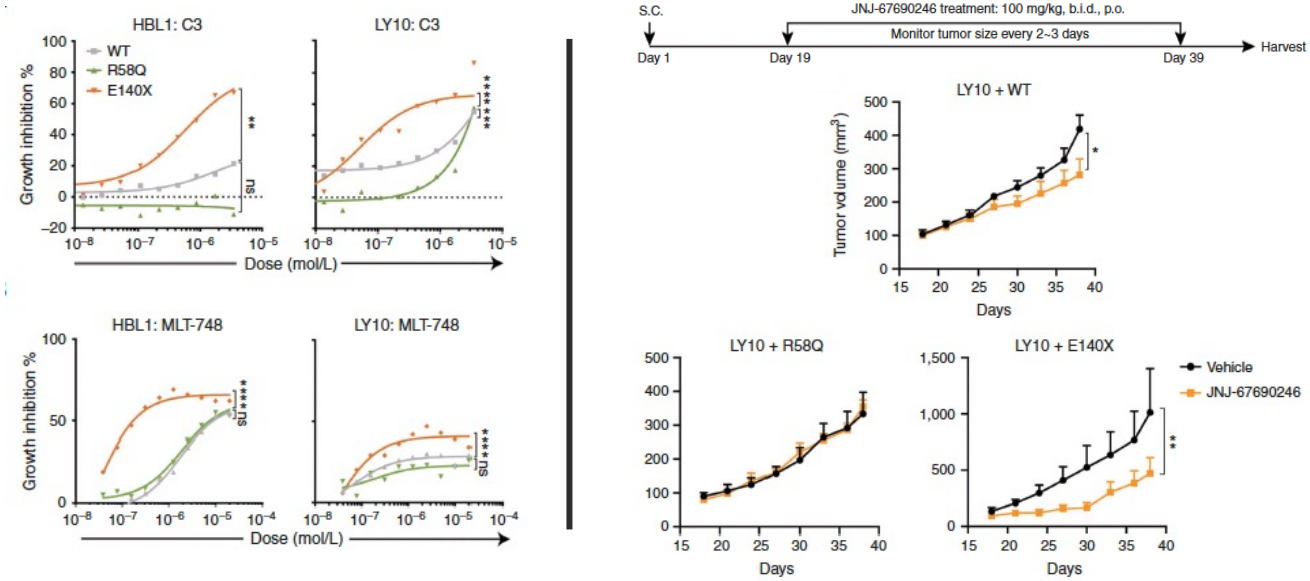

Figure 3: The truncated BCL10 mutants (E140X) demonstrated hypersensitivity to MALT1 inhibitors, whereas the missense mutants (R58Q) did not in both *in vitro* (**Left**) and *in vivo* PDX (**Right**) models.

Inventors:
Ari Melnick
Liron David
Hao Wu
Min Xia

Patents:
US Application Filed

Publications:
Xia et al. *Cancer Discov*. 2022.

Biz Dev Contact:
Brian Kelly
(646) 962-7041
bjk44@cornell.edu

Cornell Reference:
D-10374

Weill Cornell Medicine

Weill Cornell Medicine