Mutations in BCL10 as a Biomarker for Precision Therapy in DLBCL

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<th>Background &amp; Unmet Need</th>
<th>Technology Overview</th>
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<tr>
<td>• Diffuse large B-Cell Lymphoma (DLBCL) is the most common hematological malignancy</td>
<td>• The Technology: Use of BCL-10 as a biomarker to guide precision therapy for ABC DLBCL</td>
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<td>• DLBCL is classified into three subgroups, of which Activated B Cell-like (ABC) DLBCL is the most aggressive and has the poorest outcomes</td>
<td>• The Discovery: Genome sequencing revealed that mutations in BCL10 are most common in ABC-DLBCLs</td>
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<td>• Constitutive activation of NF-kB signaling is a hallmark of ABC-DLBCL, which is largely mediated by B Cell Receptor (BCR) signaling</td>
<td>• BCL10 is a part of the CBM complex, which activates NF-kB signaling downstream of BCR</td>
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<td>• BTK inhibitors have had a large impact on treatment of other lymphomas and act downstream of BCR, but show only modest effects in DLBCL</td>
<td>• Biochemical, structural, and functional analysis demonstrated that BCL10 mutations fall into two distinct classes:</td>
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<td>• 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</td>
<td>• Missense mutations in the CARD domain</td>
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<td>• Unmet Need: Better understanding of somatic mutations in ABC DLBCL to guide precision treatment selection</td>
<td>• Truncating mutations in the C-terminal</td>
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<td>• PoC Data: Both BCL10 mutants with truncating and with missense mutations demonstrate resistance to BTK inhibitors</td>
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<td>• Mutants with BCL10 truncating mutations are hypersensitive to MALT1 inhibitors, whereas missense BCL10 mutants are not</td>
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Inventors: Ari Melnick, Liron David, Hao Wu, Min Xia

Patents: Provisional Filed


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Cornell Reference: D-10374

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
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**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.

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- Liron David
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**Publications:**

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Supporting Data / Figures

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