Targeting BCMA as a Novel Therapeutic Strategy in Multiple Myeloma

Patients With Multiple Myeloma Eventually Relapse, Underscoring the Need for Novel Therapies

- Multiple myeloma (MM) is the second most common hematologic malignancy.
  - Estimated 160,000 new cases diagnosed and 106,000 deaths globally in 2018.
- Successful outcomes are hindered by the complexity of myeloma cell biology and changes to the BM microenvironment.
- While survival rates have improved in MM, almost all patients eventually relapse.

MM is Characterized by a Pattern of Recurrent Relapses

- BCMA is a transmembrane glycoprotein of the TNFR superfamily.
- BCMA is exclusively expressed on the cell membrane of late-stage B cells and plasma cells and regulates differentiation and survival of plasma cells.
  - BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue.

BCMA Is a Cell Surface Protein That Is Selectively Expressed on Mature B Lymphocytes and Plasma Cells

- BCMA membrane expression was observed in almost all samples from MM patients.

BCMA Expression During Plasma Cell Differentiation

- BCMA is highly expressed on myeloma cells.

APRIL and BAFF Are BCMA Ligands

- BCMA ligands, APRIL and BAFF, are produced in the BM microenvironment by osteoclasts, monocytes, and neutrophils.
- BCMA ligands have varying binding affinities: APRIL preferentially binds to BCMA with higher affinity than BAFF.
- APRIL and BAFF expression are increased in MM and correlate with increased BCMA expression.

BCMA Ligands and Related Receptors on Plasma Cells

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Overexpression of BCMA in myeloma cells enhances tumor growth and survival.

Upregulation of anti-apoptotic proteins (Bcl-2, Bcl-XL, and Mcl-1) and activation of the NF-kB pathway.

Upregulation of immunomodulatory proteins (eg, PD-L1, IL-10, and TGFβ), which may allow myeloma cells to evade immune detection.

Preclinical studies suggest a pro-survival role of BCMA in myeloma cells.

BCMA is a cell surface receptor expressed on mature B lymphocytes, plasma cells, and myeloma cells.

BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue.

BCMA expression is higher in myeloma cells than in normal plasma cells.

Preliminary data suggest that BCMA supports myeloma cell survival.

Amgen is currently investigating BITE® molecules designed to target BCMA.

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAF-R, BAFF receptor; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BCMA, B-cell maturation antigen; BITE, Bispesific T Cell Engager; BM, bone marrow; γ-secretase, gamma-secretase; GC, germinal center; LN, lymph node; Mcl-1, myeloid cell leukemia; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NF-kB, nuclear factor kappa-B; OS, overall survival; PC, plasma cell; PD-L1, programmed death ligand 1; PFS, progression-free survival; sBCMA, soluble BCMA; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; TGFβ, transforming growth factor β; TNFR, tumor necrosis factor receptor.

*BCMA activates growth and survival signaling cascades.*

*High sBCMA levels correlate with disease burden in patients with MM.*

*High sBCMA levels correlate with poor prognosis in patients with MM.*

*BCMA as a therapeutic target in MM.*

**BCMA signaling pathway in myeloma cells.**

**BCMA activates growth and survival signaling cascades.**

**BCMA signaling pathway in myeloma cells.**

**High sBCMA levels correlate with disease burden in patients with MM.**

**High sBCMA levels correlate with poor prognosis in patients with MM.**

**BCMA as a therapeutic target in MM.**

**Percent Survival**

<table>
<thead>
<tr>
<th>Serum BCMA (ng/mL)</th>
<th>Median OS (months):</th>
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<tbody>
<tr>
<td>Below Median</td>
<td>155 months</td>
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<tr>
<td>Above Median</td>
<td>98 months</td>
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**Overexpression of sBCMA in patient populations with MM.**

- sBCMA levels are highest in patients with active disease vs MGUS.
- sBCMA levels are lowest in those who achieve complete response and higher in those with progressive disease.

**Patients with more sBCMA demonstrate reduced PFS relative to those with lower sBCMA levels.**

**sBCMA may potentially serve as a biomarker for monitoring disease and predicting OS.**