Exploring BTK Further to Address the Specific Molecular Processes Behind B-Cell Malignancies

- Our growing understanding of the relationship between BTK and the tumor microenvironment may help to further unravel the molecular processes underlying B-cell malignancies
- Understanding these molecular processes may help guide research into resistant disease and highly targeted therapeutic strategies
- Pharmacyclics, Inc., and Janssen Biotech, Inc., are currently investigating BTK in search of insights that could improve the lives of patients with B-cell malignancies

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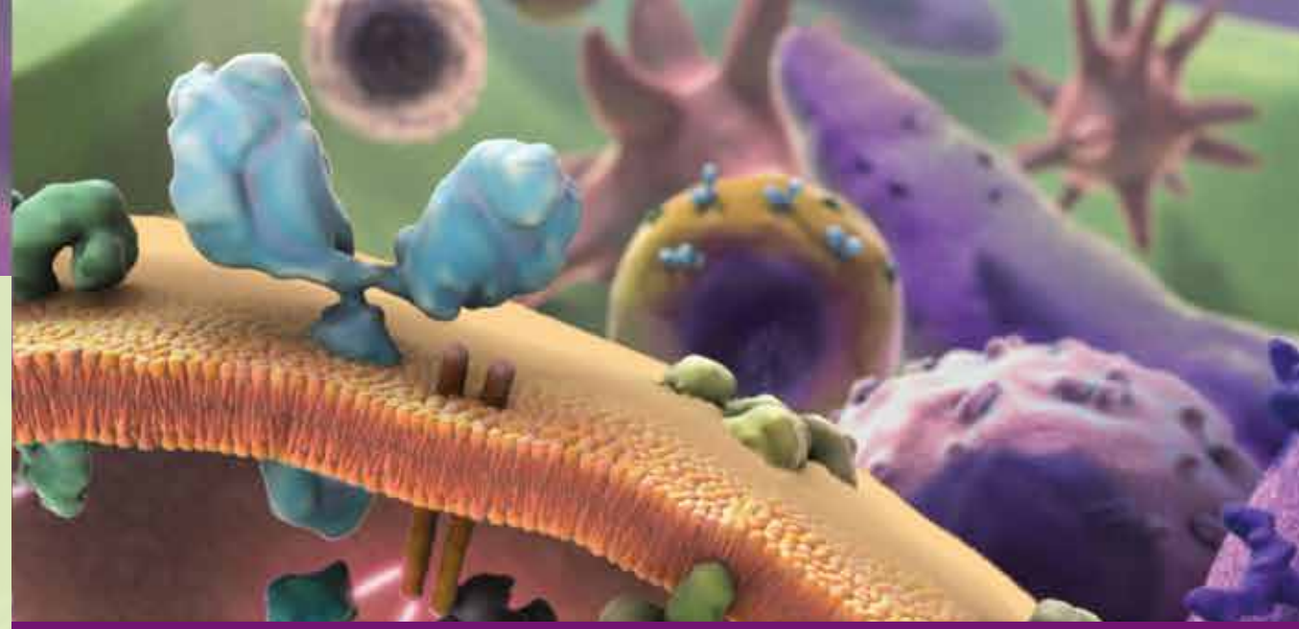

Defining new directions in B-cell malignancies*

A Critical Connection Between B-Cell Signaling and the Tumor Microenvironment

The evolving understanding of the microenvironment and Bruton's tyrosine kinase (BTK) is helping to elucidate specific molecular targets that drive B-cell malignancies.[1]

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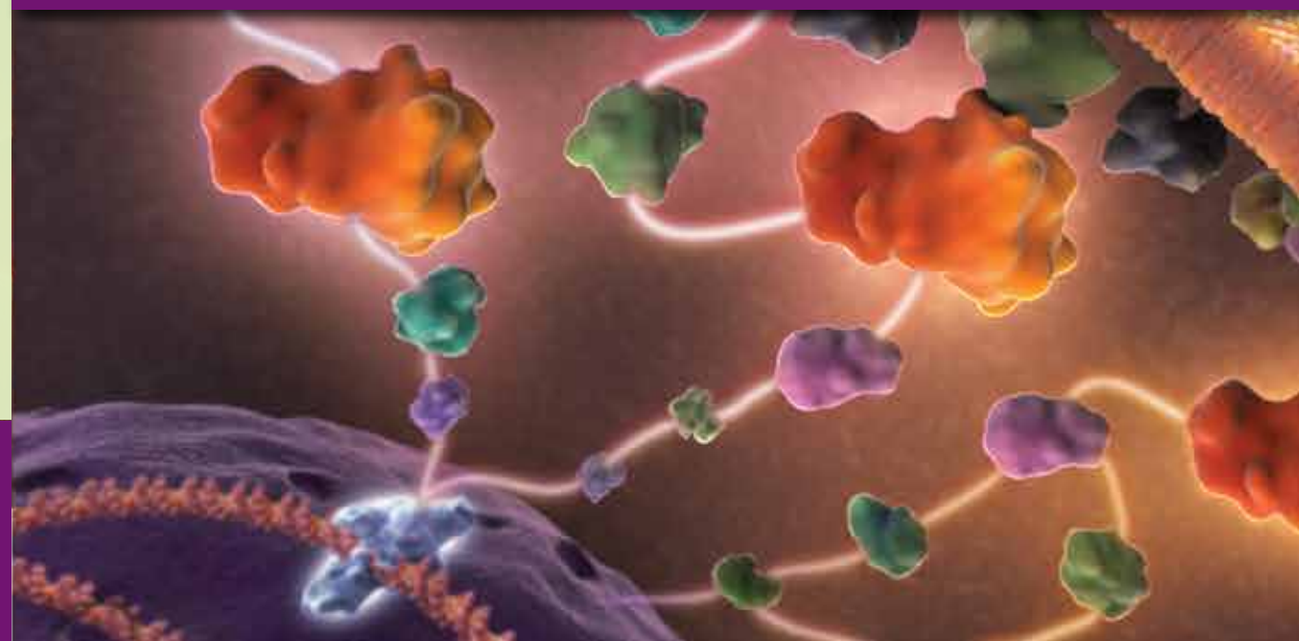
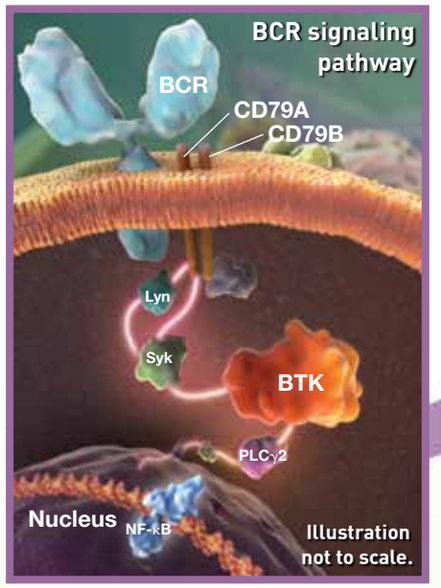


Intracellular Pathways Reliant on BTK Exploit Microenvironment Cues to Drive B-Cell Malignancies*

In B-cell malignancies, the tumor microenvironment includes the stromal cells, T cells, soluble factors, and other cells in the lymph nodes and bone marrow that continuously influence B-cell development and growth.[2] Interactions between the microenvironment and multiple signaling pathways within B cells suggest an important role in B-cell homing, adhesion, and migration, and help to maintain the normal, balanced functioning of B cells.[2,3] When the interactions become dysregulated, they can promote the progression of B-cell malignancies.[2]

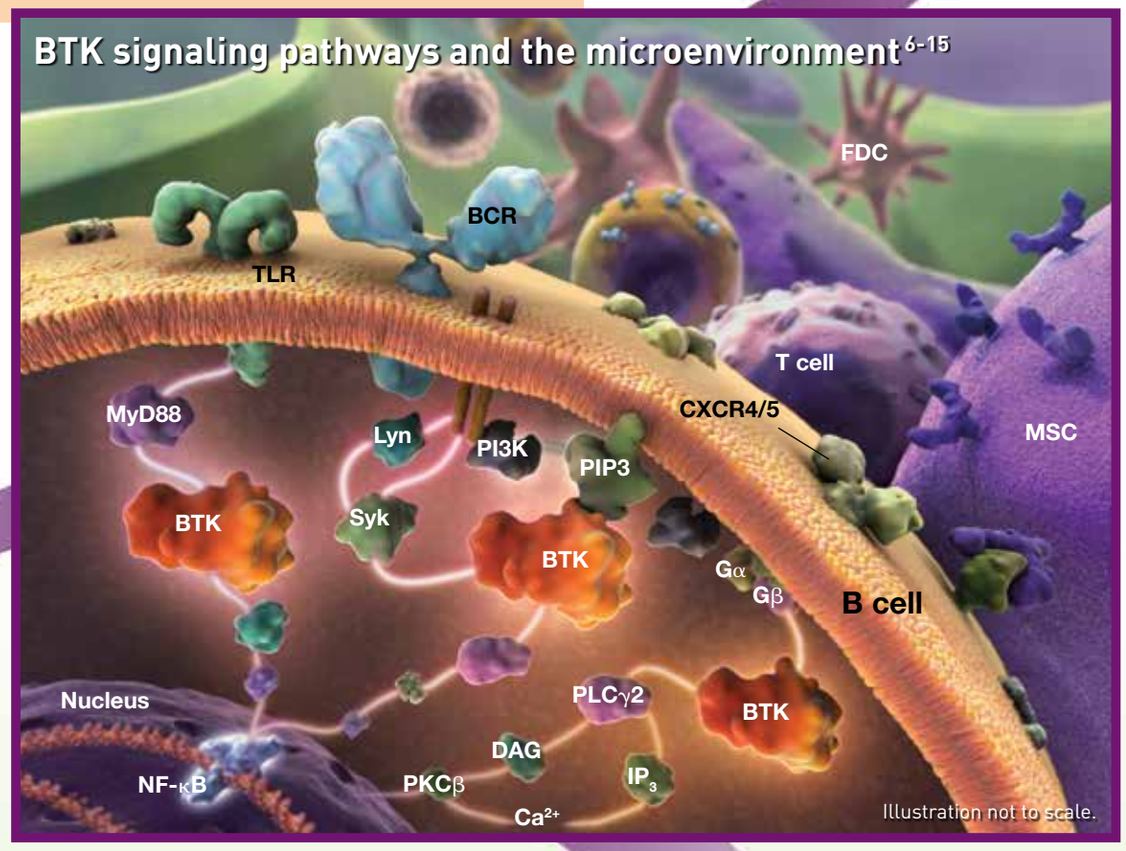
BTK, an essential component of the B-cell receptor (BCR) and other pathways, appears to play a critical role in these dysregulated interactions.[4,5]



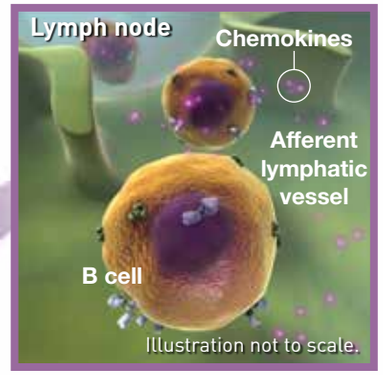
Creative representation of select simplified signaling pathways.

Prosurvival Signals[6-8,13]

Normal B cells rely on a complex network of prosurvival pathways, such as the BCR pathway, to avoid apoptosis.[16-19] In B-cell malignancies, microenvironmental cues may inappropriately activate some of these pathways.[2,20] This initiates signaling cascades through several kinases, including BTK, driving uncontrolled growth and survival of malignant B cells.[21-23]



Creative representation of select simplified signaling pathways.
*Based on in vitro data.
BAFF-R=B-cell activating factor belonging to the TNF family.
BCR=B-cell receptor.
CXCR4/5=C – X – C (motif) chemokine receptor 4, C – X – C (motif) chemokine receptor 5.
DAG=diacylglycerol.
FDC=follicular dendritic cell.
IP_3=inositol triphosphate.
MSC=mesenchymal stromal cell.
PKCβ=protein kinase C beta.
PLCγ2=phospholipase C gamma 2.
TLR=toll-like receptor.

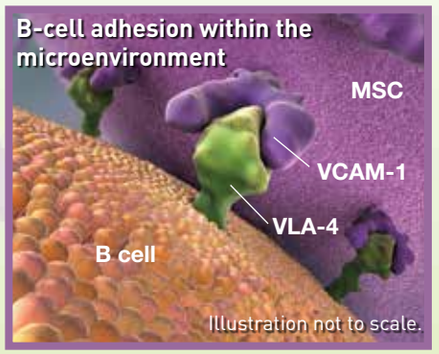


B-Cell Homing[7]

Cells in the microenvironment secrete chemoattractant factors to promote the homing of B cells to lymphoid tissue.[24] These factors act via signaling pathways involving BTK and other kinases.[3,25] In B-cell malignancies, the B cells often express factors on their surface that may further promote inappropriate homing to proliferative environments.[2,26]

Adhesion and Migration

Adhesion molecules expressed by cells in the microenvironment bind to receptors on the surface of B cells to allow them to migrate through lymphoid tissues.[3] These adhesion molecules also help to retain B cells within the lymph node microenvironment, where the B cells can proliferate.[10,27,28] BTK is an essential mediator of multiple adhesion and migration processes.[3]



In B-cell malignancies, the expression of adhesion molecules is upregulated.[26,29] This upregulation and increased migration of B cells may lead to further retention of the B cells in proliferative environments and the promotion of chemoresistance.[26,30]

VCAM-1=vascular cell adhesion molecule-1.
VLA-4=very late antigen-4.