

# Gilead Sciences: A Leader in PI3K Research in Oncology



Of the approximately 510,000 people in the United States living with non-Hodgkin's lymphoma, an estimated one-third have the indolent form of the disease (iNHL). An additional 120,000 Americans have chronic lymphocytic leukemia (CLL), another slow-growing blood cancer. Median survival for both of these cancers is 8-10 years, during which patients frequently relapse following treatment and receive multiple, different therapies in an attempt to control their disease. Typically, the remission achieved with each succeeding course of therapy becomes shorter in duration and patients' quality of life progressively declines. Additionally, the side effects of these therapies may be as debilitating as the diseases themselves. All of these factors highlight the need for new and effective therapeutic options for these cancers.

## Targeting Signaling Pathways

Conventional chemotherapy agents work by killing and inhibiting the proliferation of malignant cells. Unfortunately, standard chemotherapy may also affect other proliferating non-cancerous cells in tissues that are constantly renewing themselves, such as hair follicles (causing hair loss), blood (triggering anemia; low white cell counts, which predispose patients to infection; and low platelet counts, which may lead to bleeding) and the lining of the digestive tract (resulting in mouth sores and nausea/vomiting).

Recent advances in molecular biology, particularly the identification of signaling pathways involved in cancer, have led to new agents that target the specific molecules that help initiate and promote cancer growth.

Multiple molecular signaling pathways are involved in the development of cancer, which means that targeting one pathway is often not sufficient to improve long-term survival. Researchers are currently evaluating combinations of drugs with different mechanisms of action to determine whether a multi-pronged approach could be more effective in treating certain malignancies.

## Importance of PI3K Signaling Pathways

The understanding of the role of PI3K signaling pathways in the development of cancers, including CLL and iNHL, has advanced significantly in recent years. Phosphatidylinositol 3-kinases (PI3Ks) are a family of intracellular signaling proteins that are essential components of migratory, proliferative, survival and differentiation pathways in many cell types, including blood cells (see "About PI3K Isoforms"). Under normal circumstances, PI3K signaling pathways are strictly regulated and play an important role in the healthy functioning of cells. However, mutations and overexpression of genes involved in PI3K signaling pathways can lead to unregulated cell proliferation.

### About CLL and iNHL

#### ***Chronic lymphocytic leukemia (CLL)***

is a slow-growing cancer that primarily afflicts people over age 60 and is the most common type of leukemia in the United States. CLL induces the production of too many mature lymphocytes (white blood cells), mostly in the blood and bone marrow. It can be treated, but is not curable.

#### ***Indolent non-Hodgkin's lymphoma (iNHL)***

is also a slow-growing cancer that forms in the lymphatic system, usually in the lymph nodes, causing nodular swelling. Because lymphocytes travel throughout the body, iNHL can spread to other organs and systems. While iNHL can respond to radiation therapy and chemotherapy, most patients are diagnosed with advanced disease, which is usually not curable.

Both cancers can lead to fatigue, fever, infections, enlarged lymph nodes and other symptoms that can affect patients' physical and emotional well-being. Studies have shown that CLL and iNHL patients have a lower quality of life than the general population.

CLL and iNHL patients often require multiple courses of various therapies, potentially including chemotherapy, immunotherapy with monoclonal antibodies and radiation therapy (for iNHL). Bone marrow or stem cell transplantation is sometimes used to treat select CLL and iNHL patients.

The PI3K delta isoform is critical for the activation, proliferation and survival of B lymphocytes, a type of white blood cell that plays a central role in the immune system. PI3K delta also plays a critical role in homing and retention of B cells in lymphoid tissues. In many B cell cancers, including CLL and iNHL, hyperactive PI3K delta signaling drives malignant cells' proliferation, survival and trafficking to lymphoid tissue.

## About PI3K Isoforms

Isoforms are different forms of the same protein. They have similar functions, but each one has slight genetic differences:

- **PI3K alpha** is expressed widely in the body and is involved in insulin signaling and angiogenesis (the development of new blood vessels).
- **PI3K beta** is expressed widely and is involved in platelet function.
- **PI3K gamma** is predominantly expressed in white blood cells. It is also involved in the functioning of white blood cells called neutrophils as well as T cells.
- **PI3K delta** is also expressed in white blood cells but is mainly involved in the signaling, development and survival of B cells.

Pre-clinical studies suggest inhibiting PI3K delta may have potential as a treatment approach for these cancers, used alone or in conjunction with standard therapies or with other new targeted therapies.

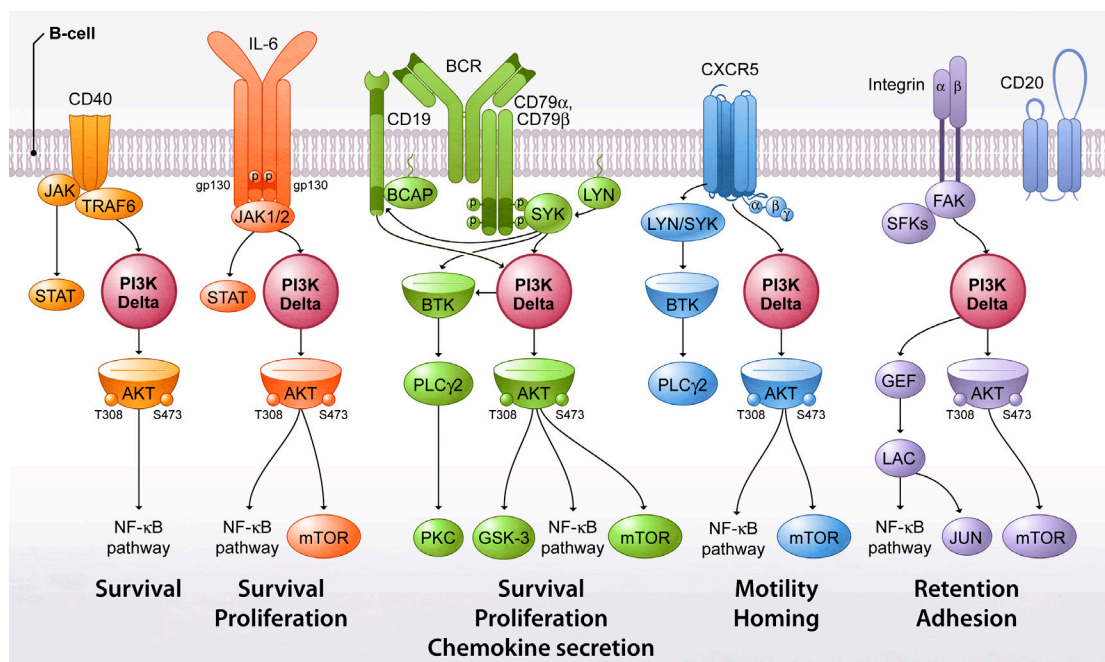
## Gilead's Focus on Oncology

Throughout its history, Gilead Sciences has focused on addressing areas of unmet medical need. The company is a leading developer of HIV therapeutics and its other areas of focus include liver disease; serious respiratory, cardiovascular and metabolic conditions; and cancer and inflammation. In recent years, Gilead has gained expertise in oncology through strategic acquisitions, new partnerships and the appointment of cancer researchers. The company is advancing a pipeline of novel investigational therapies for a range of cancers, including agents that target key intracellular signaling pathways and the cellular microenvironment involved in the development and proliferation of a variety of malignancies. Gilead recently filed for regulatory approval of an investigational oral inhibitor of PI3K delta for the treatment of iNHL and CLL in both the United States and the European Union.

## For More Information

News about Gilead's cancer research programs can be found at [www.gilead.com](http://www.gilead.com) or on Twitter (@GileadSciences). For information about Gilead's oncology clinical trials, visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov). For any additional information, please contact Gilead Public Affairs at 650-574-3000 or [public\\_affairs@gilead.com](mailto:public_affairs@gilead.com).

## PI3K Delta Signaling Pathways



*Multiple signaling pathways direct B-cell development and function. The effector molecule PI3K delta plays a central role in several of these pathways, helping to promote B-cell activation, differentiation, proliferation and survival.*