PI3K inhibitors block PI3K catalytic activity

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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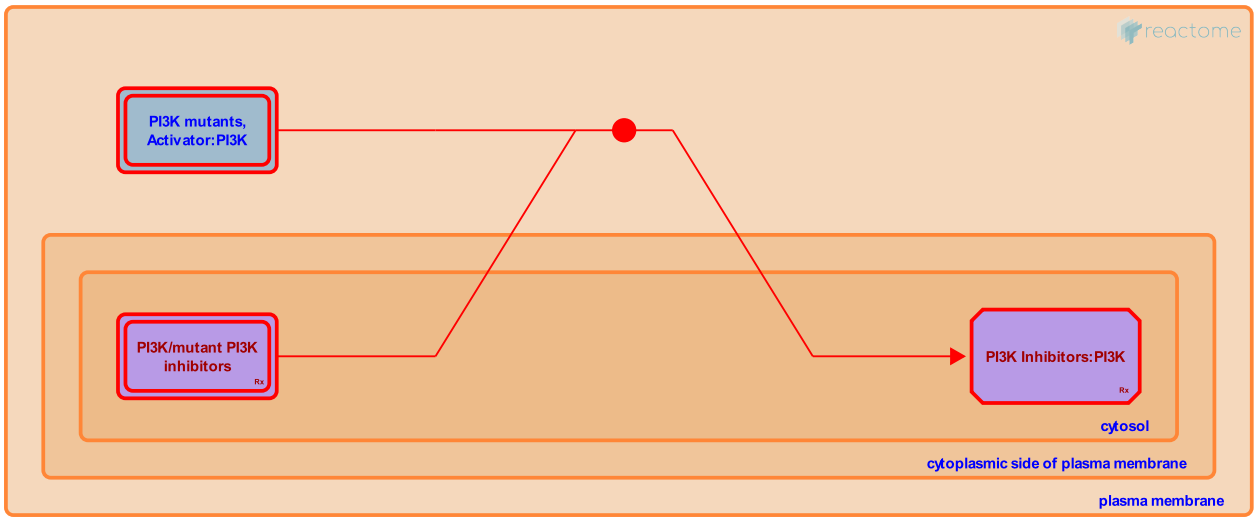
Stable identifier: R-HSA-2400009

Type: binding

Compartments: cytosol, plasma membrane, extracellular region

Diseases: cancer



A variety of inhibitors capable of blocking the phosphoinositide kinase activity of PI3K have been developed. These inhibitors display differential selectivity and inhibit kinase activity of their substrates by distinct mechanisms. For example, the first-generation PI3K inhibitor wortmannin (Wymann et al. 1996) covalently and irreversibly binds all classes of PI3K enzymes, as well as other kinases including mTOR, at a residue critical for catalytic activity. Although wortmannin is precluded from in vivo and clinical use due to its toxicity, it has proven to be a useful tool for in vitro laboratory studies. Newer inhibitors, such as BEZ235, are currently being investigated in Phase I clinical trials. BEZ235 is a dual pan-class I PI3K/mTOR inhibitor that blocks kinase activity by binding competitively to the ATP-binding pocket of these enzymes (Serra et al. 2008, Maira et al. 2008). BGT226 (Chang et al. 2011) and XL765 (Prasad et al. 2011) also inhibits both PI3K class I enzymes and mTOR. Other inhibitors in clinical trials, such as BKM120 (Maira et al. 2012), GDC0941 (Folkes et al. 2008, Junttila et al. 2009) and XL147 (Chakrabarty et al. 2012), are specific for class I PI3Ks and exhibit no activity against mTOR. Current research aims to identify isoform-specific PI3K inhibitors. Small molecule inhibitors that selectively inhibit PIK3CA (p110alpha), e.g. PIK-75 and A66, were used to study the role of p110alpha in signaling and growth of tumor cells (Knight et al. 2006, Sun et al. 2010, Jamieson et al. 2011, Utermark et al. 2012). The PIK3CB (p110beta) specific inhibitor TGX221 has been used in in vitro models of vascular injury (Jackson et al. 2005), and the TGX221 derivative KIN-193 has been shown to block AKT activity and tumor growth in mice with p110beta activation or PTEN loss (Ni et al. 2012). CAL-101 is a PIK3CD (p110delta) specific inhibitor that is being clinically investigated as a therapeutic for lymphoid malignancies (Herman et al. 2010). It is hoped that, in the future, more specific inhibitors, such as those targeting selective PI3K isoforms, will provide optimum treatment while minimizing unwanted side effects. For a recent review, please refer to Liu et al. 2009.

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Editions

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