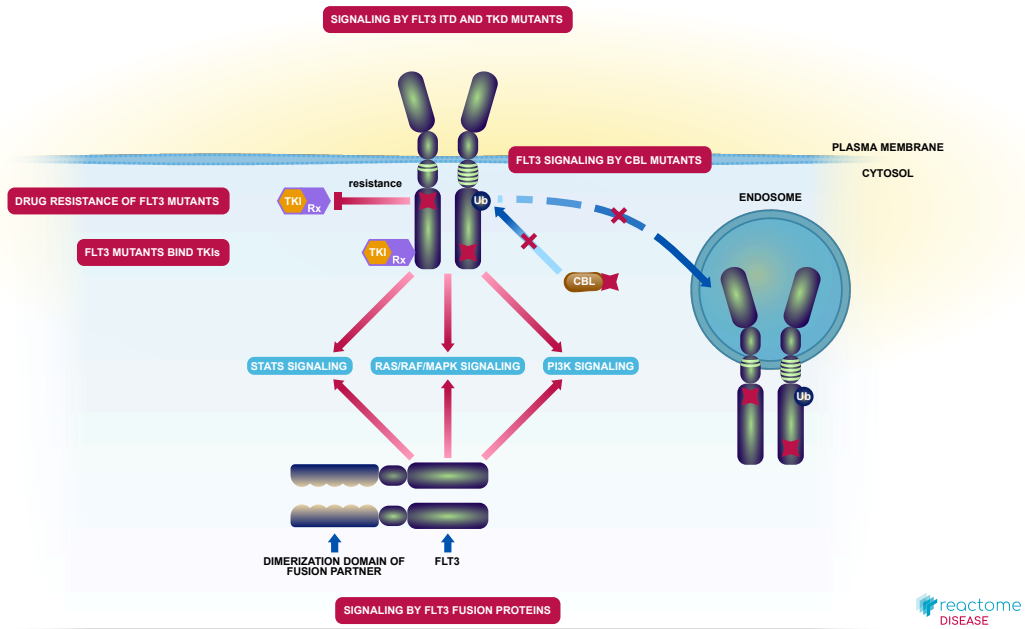
FLT3 signaling in disease



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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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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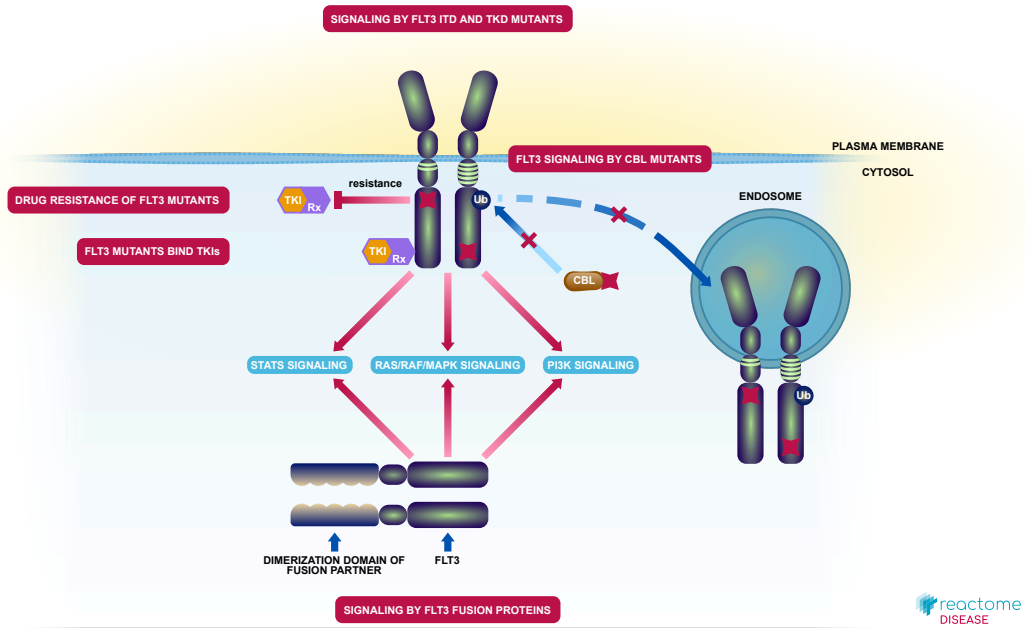
Reactome database release: 88

This document contains 6 pathways (see Table of Contents)

FLT3 signaling in disease ↗

Stable identifier: R-HSA-9682385

Diseases: cancer



FLT3 is a type III receptor tyrosine kinase (RTK). The extracellular domain consists of 5 immunoglobulin (Ig) domains that contribute to dimerization and ligand binding. The intracellular region has a juxtamembrane domain that plays a role in autoinhibiting the receptor in the absence of ligand, and a bi-lobed kinase region with an activation loop and the catalytic cleft (reviewed in Klug et al, 2018). Signaling through FLT3 occurs after ligand-induced dimerization and transautophosphorylation, and promotes signaling through the MAP kinase, PI3K and STAT5 pathways, among others. FLT3 signaling promotes cellular proliferation and differentiation and contributes to haematopoeisis. FLT3 is mutated in up to 30% of acute myeloid leukemias. ~25% of the FLT3 mutations in AML cases occur as internal tandem duplications (ITDs) either in the juxtamembrane domain region encoded by exon 14 or the tyrosine kinase domain (TKD), while ~7-10% of AML cases contain FLT3 missense mutations in the TKD (reviewed in Klug et al, 2018; Daver et al, 2019). These mutations all support ligand-independent activation of the receptor and result in constitutive activation and signaling (Zheng et al, 2004; reviewed in Klug et al, 2018; Kazi and Roonstrand, 2019). In rare cases, the FLT3 locus is also subject to translocations that generate constitutively active fusion proteins (reviewed in Kazi and Roonstrand, 2019). Oncogenic FLT3 activity can be targeted with tyrosine kinase inhibitors, although resistance often arises due to secondary mutations or activation of bypass pathways (reviewed in Staudt et al, 2018; Daver et al, 2019).

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Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

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Editions

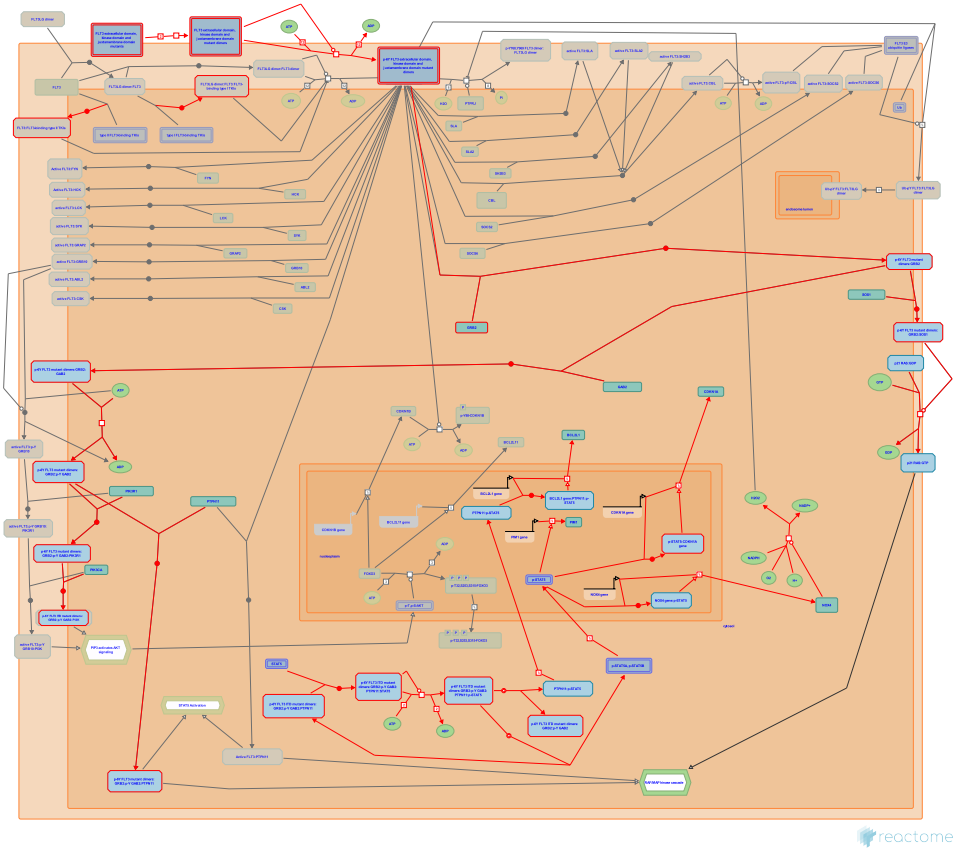
2020-11-06	Reviewed	Kazi, JU.
2020-11-06	Authored, Edited	Rothfels, K.

Signaling by FLT3 ITD and TKD mutants ↗

Location: FLT3 signaling in disease

Stable identifier: R-HSA-9703648

Diseases: cancer



FLT3 is subject to internal tandem duplications (ITDs) of lengths varying from 3 to 1236 base pairs (Nakao et al, 1996; Kiyoi et al 1997, Meshinchi et al, 2008; reviewed in Kazi and Roonstrand, 2019). These ITDs are generally found in the juxtamembrane domain, or more rarely, the first tyrosine kinase domain (TKD) and disrupt the autoinhibitory loop of the receptor, constitutively activating it (Kiyoi et al, 2002; Griffith et al, 2004; reviewed in Lagunas-Rangel and Chavez-Valencia, 2017; Kazi and Roonstrand, 2019). FLT3 ITDs are found in ~25% of acute myeloid leukemias (AMLs) and represent the most frequent mutation of this cancer (reviewed in Kazi and Roonstrand, 2019, Klug et al, 2018)
At lower frequency, FLT3 is subject to activating point mutations (~7% of AML cases). These mutations tend to cluster in the TKD, with mutation of the activation loop residue D835 and the gatekeeper F691 residue the most common sites (Griffin et al, 2001; Jiang et al, 2004; reviewed in Kazi and Roonstrand, 2019).
FLT3 ITD and TKD mutants support cellular transformation through activation of downstream signaling pathways such as the MAP kinase, PI3K/AKT and STAT5 cascades. There is some debate about the extent to which the pathways activated by the ITD and TKD mutants are distinct, with some evidence that STAT5 signaling, in particular, is more characteristic of FLT3 ITD activation (Hayakawa et al, 2000; Choudhary et al, 2005; Grundler et al, 2005; Choudhary et al, 2007; Yoshimoto et al, 2009; Leischner et al, 2012; Janke et al, 2014; Marhall et al, 2018; reviewed in Chan, 2011; Kazi and Roonstrand, 2019).

Literature references

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Editions

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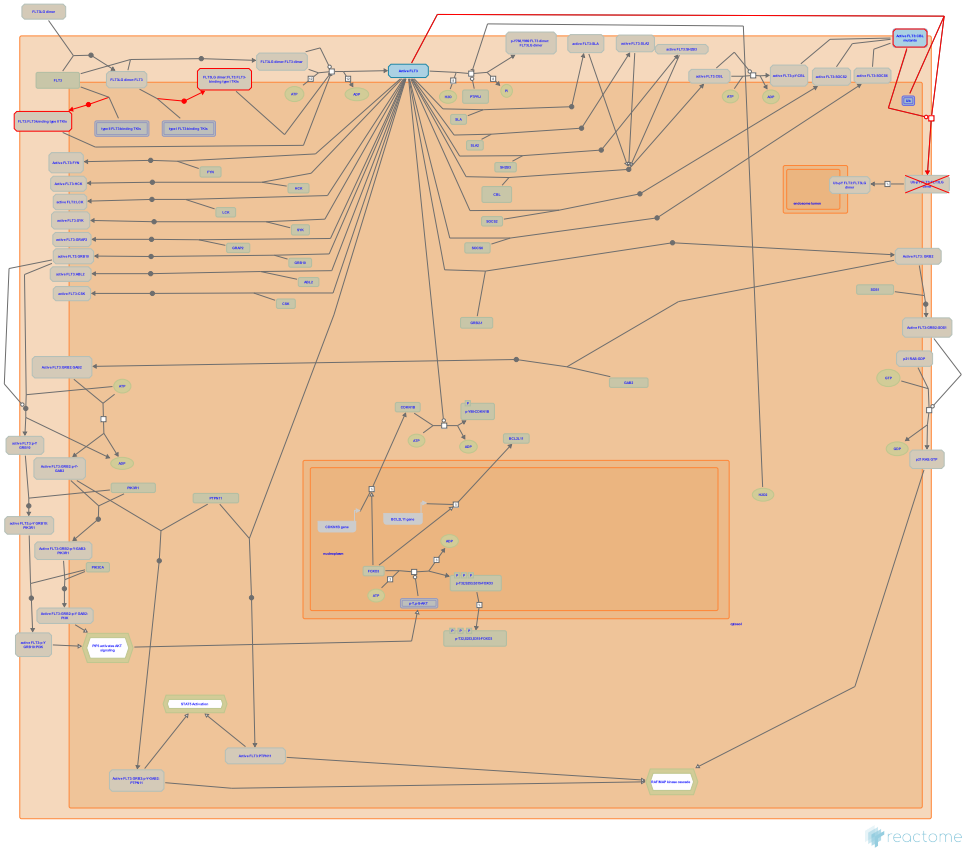
FLT3 signaling by CBL mutants ↗

Location: FLT3 signaling in disease

Stable identifier: R-HSA-9706377

Diseases: cancer



Missense and splicing mutants have been identified in the E3 ubiquitin ligase CBL in a number of cancers including acute and chronic myeloid leukemias, among others. These cancers show elevated signaling through FLT3 as a result of impaired CBL-mediated downregulation of the receptor (Sargin et al, 2007; Reindl et al, 2009; Caligiuri et al, 2007; Abbas et al, 2008).

Literature references

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Editions

2020-11-06	Reviewed	Kazi, JU.
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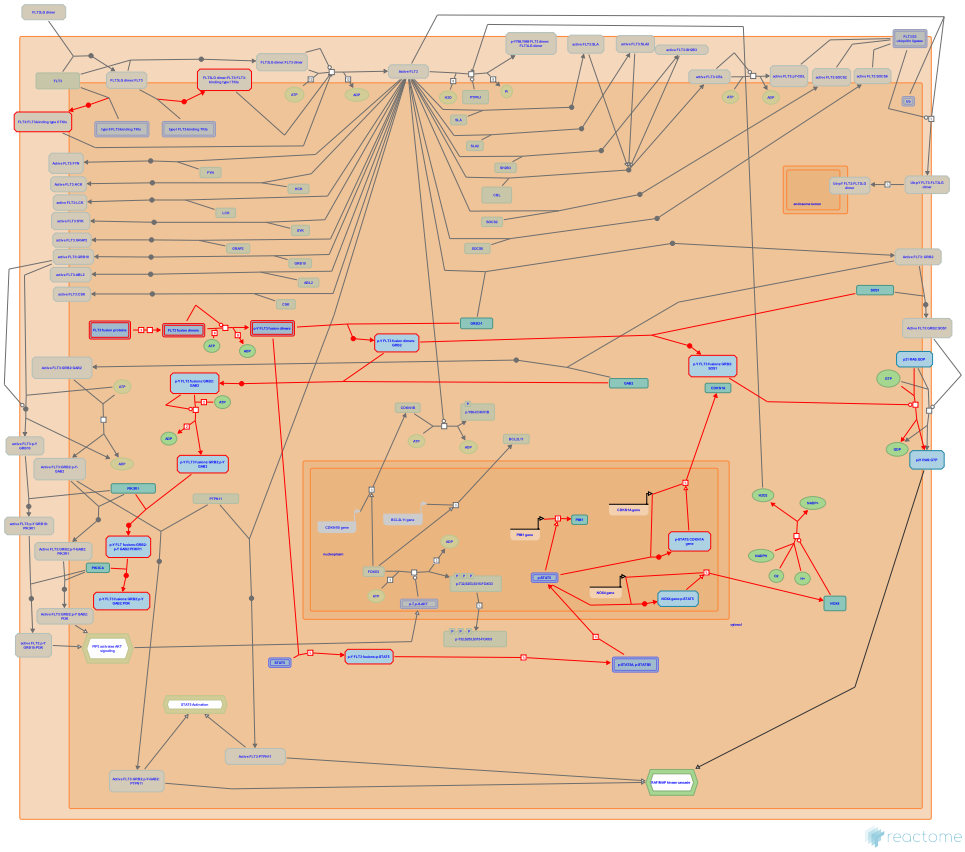
Signaling by FLT3 fusion proteins ↗

Location: FLT3 signaling in disease

Stable identifier: R-HSA-9703465

Compartments: cytosol

Diseases: cancer



In addition to internal tandem duplications and activating point mutations, FLT3 is also subject at low frequency to translocations that generate fusion proteins. These fusion proteins occur in some chronic myeloid leukemias as well as myeloid neoplasms with eosinophilia, and generate constitutively active proteins by virtue of fusing a N-terminal partner encoding a dimerization domain with the intracellular region of FLT3 (reviewed in Reiter and Gotlib, 2017; Kazi and Roonstrand, 2019). To date, 6 fusion partner genes of FLT3 have been identified: ETV6, TRIP11, MYO18A, SPTBN1, GOLGB1 and ZMYM2 (Balwin et al, 2007; Vu et al, 2006; Walz et al, 2011; Falchi et al, 2014; Chung et al, 2017; Troadec et al, 2017; Grand et al, 2007; Jawhar et al, 2017; Zhang et al, 2018).

Literature references

Jawhar, M., Tapper, W., Metzgeroth, G., Chacko, J., Score, J., Chase, A. et al. (2017). Cytogenetically cryptic ZMYM2-FLT3 and DIAPH1-PDGFRB gene fusions in myeloid neoplasms with eosinophilia, *31*, 2271-2273. ↗

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Editions

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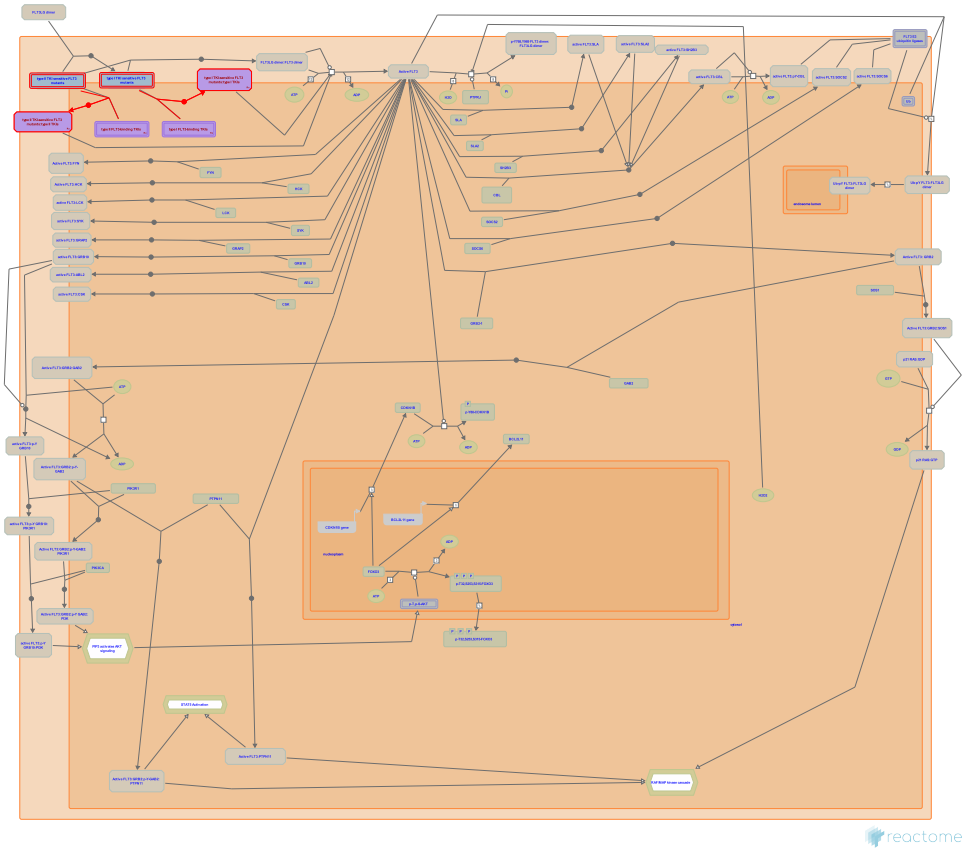
FLT3 mutants bind TKIs ↗

Location: FLT3 signaling in disease

Stable identifier: R-HSA-9702509

Compartments: plasma membrane, cytosol

Diseases: cancer



Aberrant signaling by activated forms of FLT3 can be inhibited by tyrosine kinase inhibitors (TKIs). FLT3 receptors are class III receptor tyrosine kinase receptors, also known as dual-switch. Dual-switch receptors are activated through a series of phosphorylation and conformational changes that move the receptor from the inactive form to the fully activated form. Type II TKIs bind to the inactive form of the receptor at a site adjacent to the ATP-binding cleft, while type I TKIs bind to the active form (reviewed in Klug et al, 2018; Daver et al, 2019).

FLT3 internal tandem duplications (ITDs) are found in ~25-30% of acute myeloid leukemias, and are present at lower frequencies in other cancers (reviewed in Kazi and Roostrand, 2019; Patnaik et al, 2018). These ITDs generally occur in a tyrosine-rich region of exon 14, encoding the juxtamembrane domain region of the protein; at a lower frequency, ITDs are found in the first tyrosine kinase domain (TKD1). In addition to ITDs, a number of point mutations in the juxtamembrane domain have also been identified. Juxtamembrane domain mutations affect an autoinhibitory loop, shifting the equilibrium of the receptor towards the activated state; despite this, however, juxtamembrane domain mutants remain predominantly in the inactive state and as such are susceptible to inhibition by type II TKIs (reviewed in Patnaik et al, 2018; Kazi and Roonstrand et al, 2019).

Activation loop mutations more strongly favor the active conformation of the receptor and are susceptible to inhibition by both type II and type I TKIs. The most prevalent FLT3 mutation, D835Y, promotes the active conformation strongly enough to be resistant to type II TKIs (Patnaik et al, 2017; Klug et al, 2018; Daver et al, 2019).

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Kazi, JU., Rönnstrand, L. (2019). FMS-like Tyrosine Kinase 3/FLT3: From Basic Science to Clinical Implications. *Physiol. Rev., 99*, 1433-1466. ↗

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Editions

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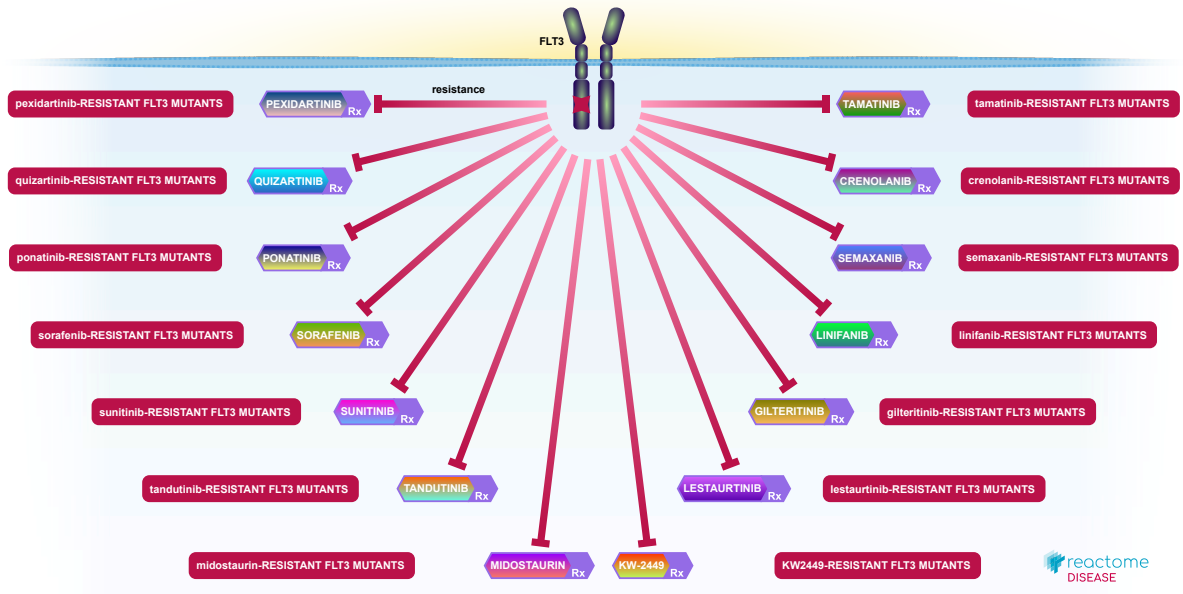
2020-11-06	Authored, Edited	Rothfels, K.

Drug resistance of FLT3 mutants ↗

Location: FLT3 signaling in disease

Stable identifier: R-HSA-9702506

Diseases: cancer



FLT3 is mutated in ~30% of acute myeloid leukemias (AML), with internal tandem duplications (ITDs) representing the majority of these mutations and activating point mutants occurring at lower frequency. FLT3 mutations also occur at lower rates in other cancers (reviewed in Kazi and Roonstrand, 2018; Daver et al, 2019; Larroas-Garcia and Baer, 2017). Mutation of FLT3 has been identified as a driver in progression of AML and in consequence is a promising therapeutic target. A number of first and second generation inhibitors have been demonstrated to have activity against FLT3, but accumulation of secondary mutations leads to the development of resistance. These secondary mutations further shift the equilibrium of the receptor toward the activated state, making even the second-generation type II TKIs less effective. In consequence, considerable effort is devoted to discovery of type II and, in particular, type I TKIs that are active against highly activated FLT3 alleles (reviewed in Daver et al, 2019; Staudt et al, 2018; Lim et al, 2017; Klug et al, 2018).

Literature references

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Editions

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