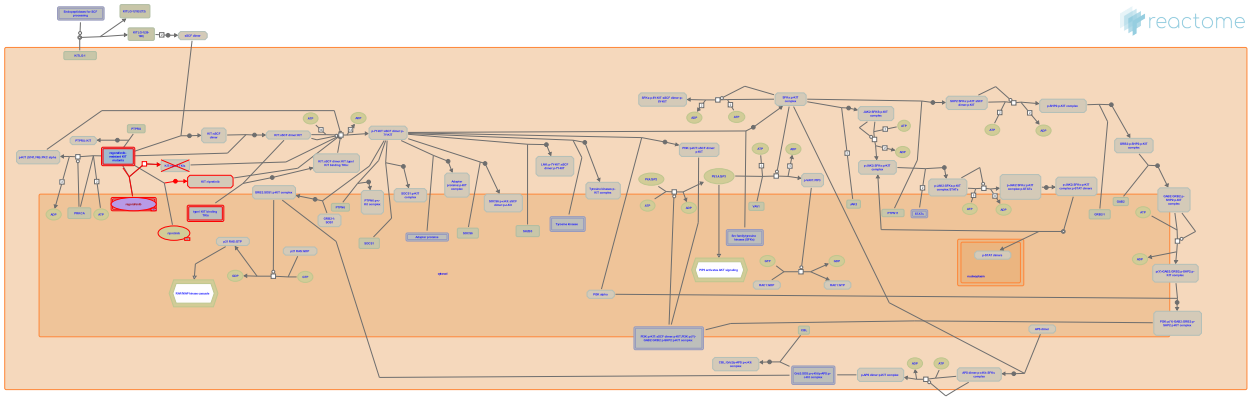
Regorafenib-resistant KIT mutants



García-Valverde, A., Pilco-Janeta, D., Rothfels, K., Serrano, C.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

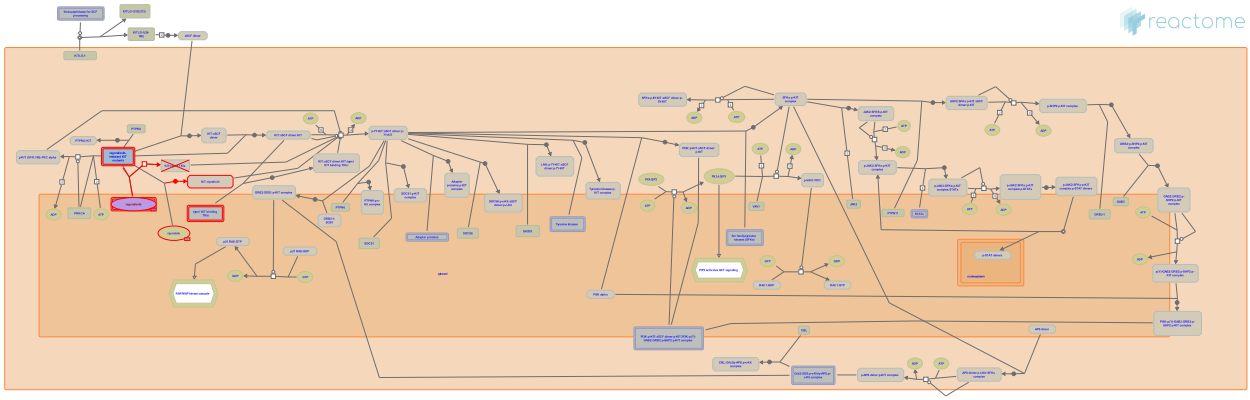
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Regorafenib-resistant KIT mutants ↗

Stable identifier: R-HSA-9669929

Diseases: cancer



Regorafenib is a type II tyrosine kinase inhibitor that is approved for treatment of advanced gastrointestinal stromal tumors with KIT mutations. Regorafenib is effective in imatinib-resistant tumors carrying secondary mutations in exon 14 (gatekeeper mutation), and most KIT secondary mutations encoded by exons 17 and 18 (the activation loop) (Demetri et al, 2013; Serrano et al, 2017, Serrano et al, 2019; reviewed in Roskoski, 2018; Klug et al, 2018;).

Literature references

Morales-Barrera, R., Carles, J., Suárez, C., García-Valverde, A., Olivares, D., Valverde, C. et al. (2017). Novel Insights into the Treatment of Imatinib-Resistant Gastrointestinal Stromal Tumors. *Target Oncol, 12*, 277-288. ↗

Roskoski, R. (2018). The role of small molecule Kit protein-tyrosine kinase inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 133*, 35-52. ↗

Heinrich, MC., Ketzer, J., Bauer, S., Zhu, M., Presnell, A., Raut, CP. et al. (2019). Complementary activity of tyrosine kinase inhibitors against secondary kit mutations in imatinib-resistant gastrointestinal stromal tumours. *Br. J. Cancer, 120*, 612-620. ↗

Heinrich, MC., Kent, JD., Klug, LR. (2018). Structural and clinical consequences of activation loop mutations in class III receptor tyrosine kinases. *Pharmacol. Ther., 191*, 123-134. ↗

Joensuu, H., Silberman, SL., Capdeville, R., Peng, B., Heinrich, MC., Singer, S. et al. (2002). Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N. Engl. J. Med., 347*, 472-80. ↗

Editions

2020-03-13	Reviewed	Serrano, C., Pilco-Janeta, D., García-Valverde, A.
2020-04-01	Authored	Rothfels, K.
2020-05-04	Edited	Rothfels, K.

Regorafenib-resistant KIT mutants do not bind regorafenib ↗

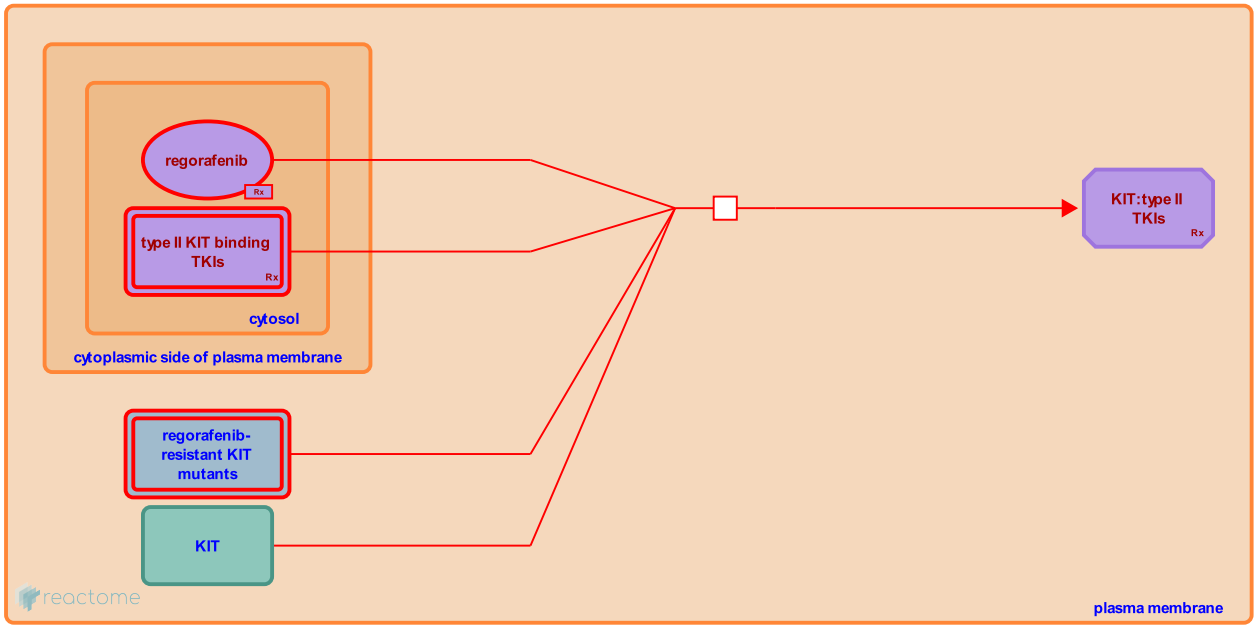
Location: Regorafenib-resistant KIT mutants

Stable identifier: R-HSA-9669870

Type: transition

Compartments: plasma membrane

Diseases: cancer



Regorafenib is used as a secondary therapeutic in cases of imatinib-resistant cancers with KIT mutations. Its effectiveness depends on the position of the secondary mutation. Regorafenib is effective in imatinib-resistant tumors carrying secondary mutations in exon 14 (gatekeeper) and most secondary mutations encoded by exons 17 and 18 (activation loop) (Yeh et al, 2017; Miyake et al, 2018; Serrano et al, 2019a,b; reviewed in Roskoski, 2018; Klug et al, 2018).

Literature references

Tzen, CY., Chen, MH., Chen, YY., Yang, CY., Yen, CC., Yeh, CN. et al. (2017). A phase II trial of regorafenib in patients with metastatic and/or a unresectable gastrointestinal stromal tumor harboring secondary mutations of exon 17. *Oncotarget, 8*, 44121-44130. ↗

Miyake, K., Momiyama, M., Eilber, FC., Murakami, T., Russell, T., Miyake, M. et al. (2018). Regorafenib regresses an imatinib-resistant recurrent gastrointestinal stromal tumor (GIST) with a mutation in exons 11 and 17 of c-kit in a patient-derived orthotopic xenograft (PDOX) nude mouse model. *Cell Cycle, 17*, 722-727. ↗

Roskoski, R. (2018). The role of small molecule Kit protein-tyrosine kinase inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res., 133*, 35-52. ↗

Heinrich, MC., Ketzer, J., Bauer, S., Zhu, M., Presnell, A., Raut, CP. et al. (2019). Complementary activity of tyrosine kinase inhibitors against secondary kit mutations in imatinib-resistant gastrointestinal stromal tumours. *Br. J. Cancer, 120*, 612-620. ↗

Heinrich, MC., Kent, JD., Klug, LR. (2018). Structural and clinical consequences of activation loop mutations in class III receptor tyrosine kinases. *Pharmacol. Ther., 191*, 123-134. ↗

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