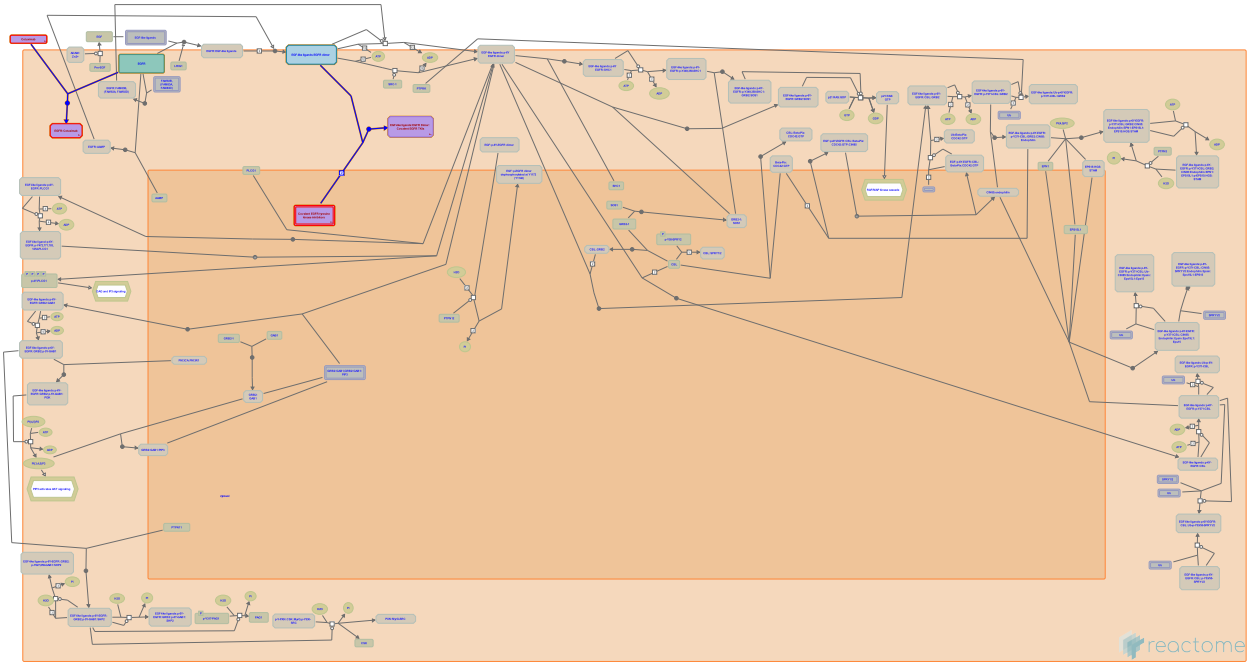
Inhibition of Signaling by Overexpressed EGFR



D'Eustachio, P., Gillespie, ME., Greulich, H., Haw, R., Jassal, B., Matthews, L., Orlic-Milacic, M., Savas, S., Wu, G.

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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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

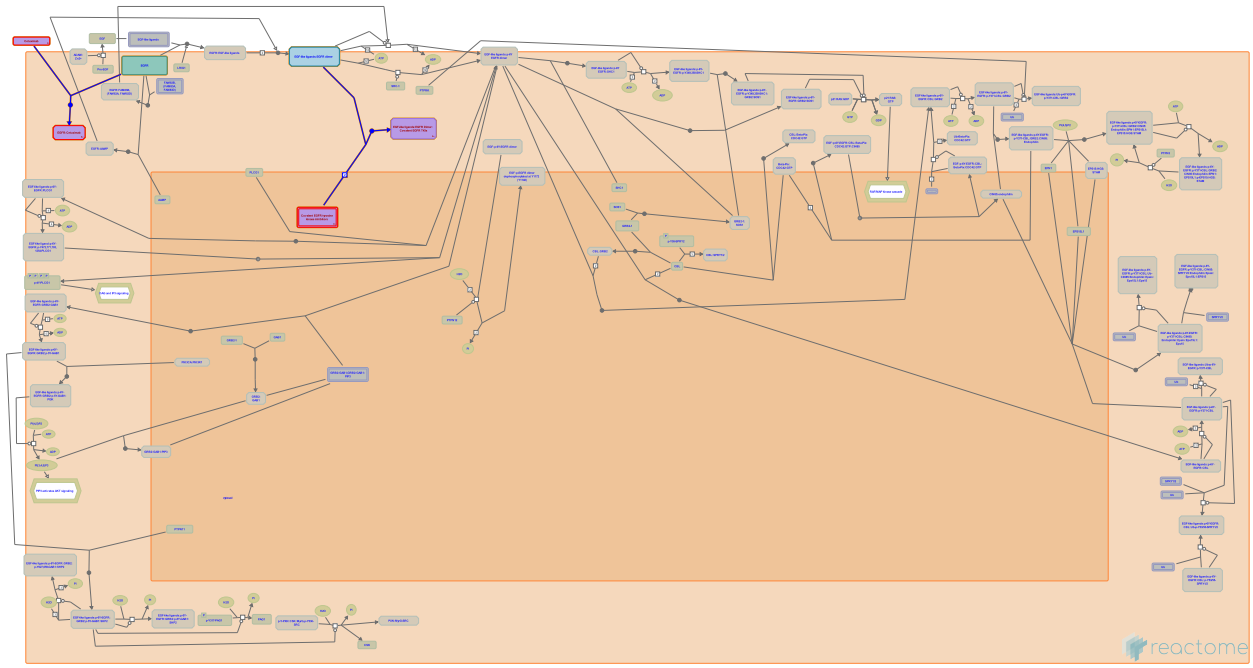
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Inhibition of Signaling by Overexpressed EGFR ↗

Stable identifier: R-HSA-5638303

Diseases: cancer



Recombinant monoclonal antibody Cetuximab acts as an antagonist of EGFR ligand binding, and is approved for the treatment of tumors that over-express wild-type EGFR receptor (Cunningham et al. 2004, Li et al. 2005, Burtness et al. 2005). Effective concentrations of covalent tyrosine kinase inhibitors (TKIs) inhibit wild-type EGFR, causing severe side effects (Zhou et al. 2009). Hence, covalent TKIs have not shown much promise in clinical trials (Reviewed by Pao and Chmielecki in 2010).

Literature references

Bleiberg, H., Humblet, Y., Mueser, M., Khayat, D., Chau, I., Cunningham, D. et al. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med, 351*, 337-45. ↗

Zhou, W., Eck, MJ., Cortot, AB., Jänne, PA., Capelletti, M., Li, D. et al. (2009). Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature, 462*, 1070-4. ↗

Ferguson, KM., Wiltzius, JJW., Schmitz, KR., Li, S., Kussie, P., Jeffrey, PD. (2005). Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell, 7*, 301-11. ↗

Forastiere, AA., Burtness, B., Eastern Cooperative Oncology, Group., Flood, W., Goldwasser, MA., Mattar, B. (2005). Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol, 23*, 8646-54. ↗

Chmielecki, J., Pao, W. (2010). Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer, 10*, 760-74. ↗

Editions

2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	Jassal, B., Gillespie, ME., Wu, G., D'Eustachio, P., Matthews, L., Haw, R.
2011-11-15	Reviewed	Greulich, H., Savas, S.

Inactivation of over-expressed wild type EGFR by Cetuximab recombinant antibody

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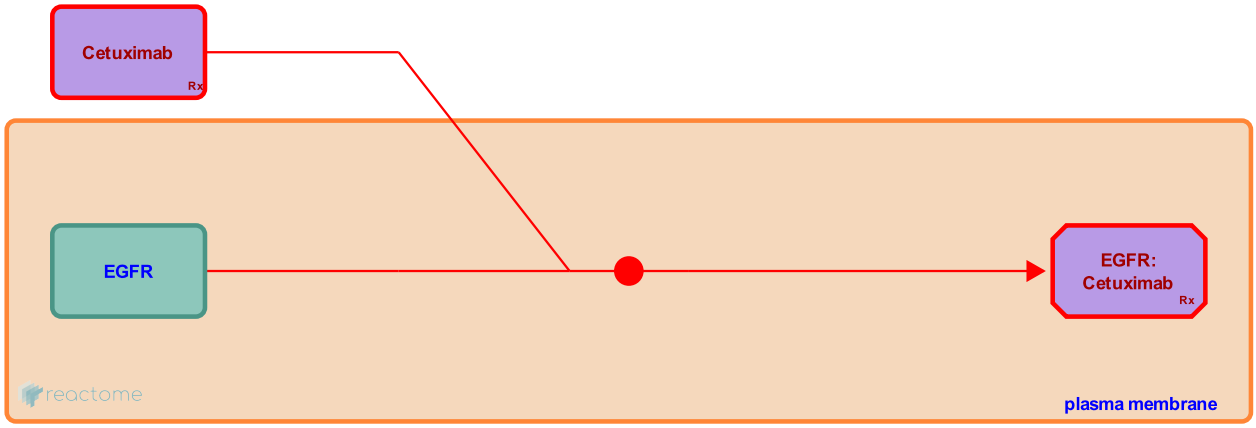
Location: Inhibition of Signaling by Overexpressed EGFR

Stable identifier: R-HSA-1248677

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: cancer, head and neck squamous cell carcinoma, large intestine cancer



Cetuximab binds to the extracellular domain of EGFR and blocks ligand binding, leading to receptor inactivation, internalization and degradation. Cetuximab is approved for combination therapy and monotherapy of metastatic colorectal cancer and advanced squamous cell carcinoma of head and neck in patients whose tumors over-express wild-type EGFR protein, usually due to amplification of EGFR gene.

Literature references

Bleiberg, H., Humblet, Y., Mueser, M., Khayat, D., Chau, I., Cunningham, D. et al. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med, 351*, 337-45. ↗

Ferguson, KM., Wiltzius, JJW., Schmitz, KR., Li, S., Kussie, P., Jeffrey, PD. (2005). Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell, 7*, 301-11. ↗

Forastiere, AA., Burtness, B., Eastern Cooperative Oncology, Group., Flood, W., Goldwasser, MA., Mattar, B. (2005). Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol, 23*, 8646-54. ↗

Editions

2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	Wu, G., D'Eustachio, P., Matthews, L.
2011-11-15	Reviewed	Greulich, H., Savas, S.

Covalent tyrosine kinase inhibitors bind and inhibit wild-type EGF:EGFR dimers

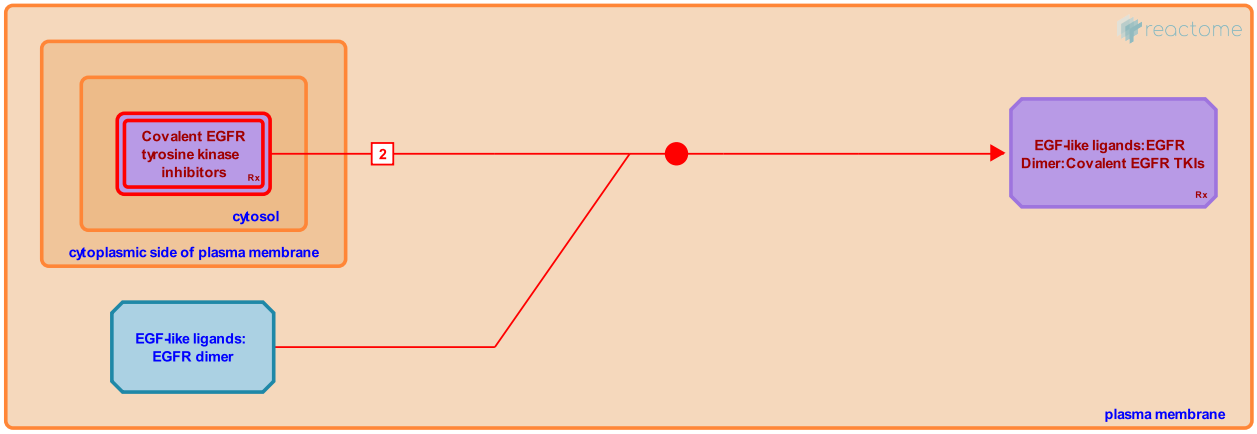
Location: Inhibition of Signaling by Overexpressed EGFR

Stable identifier: R-HSA-1225978

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cancer



Covalent (irreversible) TKIs, pelitinib, WZ4002, HKI-272, canertinib and afatinib, inhibit the wild-type EGFR through formation of the covalent bond with the cysteine residue C397.

Literature references

Zhou, W., Eck, MJ., Cortot, AB., Jänne, PA., Capelletti, M., Li, D. et al. (2009). Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature, 462*, 1070-4.

Editions

2011-11-04	Authored	Orlic-Milacic, M.
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