1. Phylogeny  
   ERBB4, also known as HER4 or c-ErbB-4, is a member of the ErbB family of receptor tyrosine kinases. This family comprises four related proteins—ERBB1 (EGFR), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4)—which share a common evolutionary origin and conserved domain architecture. ERBB4 is conserved across vertebrate species and is detected in a wide range of tissues, underscoring its essential role in normal embryonic development and postnatal physiology (OpenTargets Search: -ERBB4, qiu2008mechanismofactivation pages 1-2). Phylogenetically, ERBB4 is classified under the receptor tyrosine kinase family often traced back to ancestral metazoans, and its structure and sequence similarities with other ErbB members indicate that gene duplication events early in metazoan evolution contributed to the expansion and specialization of this receptor family (OpenTargets Search: -ERBB4). In evolutionary terms, ERBB4 is distinguished by its ability to form homodimers as well as heterodimers with other ErbB receptors, a feature that is conserved across its orthologs present in mammals and other vertebrates (qiu2008mechanismofactivation pages 1-2).

Studies have demonstrated that while all ErbB family members share the basic hallmark of an extracellular ligand-binding region, a single transmembrane helix, and an intracellular tyrosine kinase domain, ERBB4 maintains unique regulatory elements that have been conserved throughout evolution. Its capacity for binding a distinct set of ligands—including neuregulins (NRG1–4) and several members of the EGF family such as BTC, EREG, and HBEGF—enables context‐specific activities during organ development and cell differentiation. The evolutionary conservation of these ligand–receptor relationships highlights the critical role of ERBB4 in the orchestration of pathways that govern tissue morphogenesis and cellular communication (OpenTargets Search: -ERBB4, qiu2008mechanismofactivation pages 1-2). Furthermore, the diversity of isoforms generated from ERBB4 through alternative splicing is an evolutionarily conserved mechanism that extends the functional repertoire of this receptor, allowing fine-tuning of its signaling in specific tissues such as the heart, central nervous system, and mammary gland (OpenTargets Search: -ERBB4).

1. Reaction Catalyzed  
   As a receptor tyrosine kinase, ERBB4 catalyzes the transfer of a phosphoryl group from ATP to tyrosine residues on substrate proteins. The overall chemical reaction can be summarized as follows:  
     ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺  
   This reaction encompasses both autophosphorylation of the receptor upon ligand-induced activation and the phosphorylation of downstream signaling proteins. The phosphorylation events create docking sites for SH2 and PTB domain–containing adaptor proteins, which initiate further signaling cascades within the cell (qiu2008mechanismofactivation pages 1-2, wu2015fdaapprovedsmallmoleculekinase pages 30-34).
2. Cofactor Requirements  
   The catalytic activity of ERBB4, like that of most kinases, depends on divalent cations to facilitate ATP binding and phosphoryl transfer. In particular, Mg²⁺ acts as an essential cofactor for the kinase reaction by coordinating with the ATP molecule, thereby stabilizing its structure in the active site of the kinase domain. This requirement for Mg²⁺ is typical among tyrosine kinases and is fundamental to the efficient catalytic activity of ERBB4 (wu2015fdaapprovedsmallmoleculekinase pages 1-6, qiu2008mechanismofactivation pages 1-2).
3. Substrate Specificity  
   ERBB4 exhibits substrate specificity that is characteristic of receptor tyrosine kinases. Its primary substrates include the receptor itself, through autophosphorylation, which then creates binding sites for downstream effector proteins. Key phosphorylated tyrosine residues in the intracellular C-terminal tail form specific docking motifs for SH2 and PTB domain–containing proteins such as the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) (OpenTargets Search: -ERBB4, wee2017epidermalgrowthfactor pages 11-13). Experimentally, synthetic peptide substrates—such as those used in kinase assays with sequences like GGME-DIYFEFMGGKKK—have demonstrated that ERBB4 has robust catalytic activity with moderate substrate affinity, although no single consensus motif has been universally defined. Instead, the enzyme’s substrate specificity appears to be governed by the local amino acid environment around the target tyrosine residues, enabling efficient recruitment of a variety of downstream signaling molecules that ultimately propagate cellular responses (qiu2008mechanismofactivation pages 3-5).
4. Structure  
   ERBB4 displays a modular structure composed of distinct regions that are crucial for its function. The extracellular portion of the receptor is organized into four subdomains; domains I and III consist of leucine-rich repeats that are involved in ligand binding, while domains II and IV are cysteine-rich and mediate receptor dimerization. In the absence of a ligand, this extracellular region typically adopts an autoinhibited conformation, which is relieved upon ligand binding to facilitate the formation of receptor dimers (qiu2008mechanismofactivation pages 1-2, wee2017epidermalgrowthfactor pages 3-5).

The transmembrane domain constitutes a single α-helical segment that anchors ERBB4 in the plasma membrane and contributes to dimerization through specific helix-helix interactions. Intracellularly, the receptor contains a well-defined tyrosine kinase domain that is flanked by regulatory regions. This catalytic domain is composed of an N-terminal lobe rich in β-sheets and a predominantly α-helical C-terminal lobe. Key structural features of the kinase domain include the ATP-binding pocket, an activation loop that undergoes conformational rearrangements upon activation, and a conserved αC-helix that contributes to the formation of the active site (qiu2008mechanismofactivation pages 3-5, qiu2008mechanismofactivation pages 6-7).

Crystallographic studies have revealed that ERBB4 can adopt both active and inactive conformations. In the active state, the kinase domain forms an asymmetric dimer in which one kinase domain acts in an “activator” role and the other as a “receiver,” thereby promoting transautophosphorylation at critical tyrosine residues. This dimer assembly is similar to that observed in EGFR and is essential for full catalytic activation (qiu2008mechanismofactivation pages 7-8, wee2017epidermalgrowthfactor pages 37-39). In addition, alternative splice variants of ERBB4 result in isoforms with divergent cytoplasmic tails; for example, the Cyt1 isoform contains a region including Tyr1056 that is important for growth inhibitory functions and differentiation in mammary epithelial cells (OpenTargets Search: -ERBB4). Overall, ERBB4’s structure reflects a sophisticated design in which distinct domains mediate ligand recognition, receptor dimerization, and regulated kinase activity (qiu2008mechanismofactivation pages 7-8, wee2017epidermalgrowthfactor pages 41-42).

1. Regulation  
   The regulation of ERBB4 is complex, involving multiple layers of control that ensure context-dependent signaling. Ligand binding to the extracellular domain is the primary trigger for its activation; binding of neuregulins (NRG1–NRG4) and EGF family ligands such as betacellulin (BTC), epiregulin (EREG), and heparin-binding EGF (HBEGF) induces conformational changes that promote receptor dimerization. Dimerization may occur between ERBB4 molecules (homodimerization) or between ERBB4 and other ErbB family members (heterodimerization), with the dimeric context greatly influencing the downstream signaling outcome. Homodimers of ERBB4 are often associated with tumor suppressor activities, whereas heterodimers with EGFR or ERBB2 are typically linked to oncogenic signaling (qiu2008mechanismofactivation pages 1-2, wee2017epidermalgrowthfactor pages 25-27).

Post-translational modifications play a central role in modulating ERBB4 activity. Autophosphorylation upon dimerization creates phosphotyrosine motifs that serve as docking sites for signaling adapters and effectors; these phosphorylation events are essential both for signal propagation and for providing feedback regulation of receptor activity (qiu2008mechanismofactivation pages 5-6). In addition, specific phosphorylation events within the kinase domain influence the stabilization of the active conformation and facilitate asymmetric dimer formation, as demonstrated by crystallographic studies (qiu2008mechanismofactivation pages 6-7).

Regulation of ERBB4 is further modulated by proteolytic processing. ADAM metalloproteinases such as ADAM17 are implicated in the ectodomain shedding of ERBB family receptors, a process that can modulate receptor availability and function at the cell surface; this proteolytic cleavage is regulated by phosphorylation, with kinase cascades such as those mediated by ERK playing a role in controlling ADAM activity (edwards2008theadammetalloproteinases pages 30-31, seals2003theadamsfamily pages 9-10). The generation of intracellular fragments (such as the 4ICD) through regulated intramembrane proteolysis adds another dimension to ERBB4 regulation by enabling nuclear signaling that may contribute to transcriptional control (OpenTargets Search: -ERBB4). Together, these regulatory mechanisms—including ligand-induced dimerization, autophosphorylation, and proteolytic processing—ensure that ERBB4 activity is tightly controlled in both developmental and pathological contexts (qiu2008mechanismofactivation pages 5-6, wee2017epidermalgrowthfactor pages 25-27).

1. Function  
   ERBB4 functions as a cell surface receptor that binds neuregulins and a subset of EGF family members, playing crucial roles in a diverse array of biological processes. Its expression is particularly prominent in tissues such as the heart, central nervous system, and mammary gland, where it is essential for proper organogenesis and function. In the developing heart, ERBB4 is required for normal cardiac muscle differentiation and postnatal cardiomyocyte proliferation, ensuring the formation of a functional myocardium during embryogenesis and contributing to tissue maintenance after birth (OpenTargets Search: -ERBB4, wee2017epidermalgrowthfactor pages 25-27). In the central nervous system, ERBB4 is critical for neural crest cell migration, axon guidance, and overall proper neural development. Moreover, in the mammary gland, ERBB4 is required for gland differentiation, the induction of milk protein expression, and effective lactation (OpenTargets Search: -ERBB4).

Upon ligand binding and subsequent receptor dimerization, ERBB4 undergoes autophosphorylation on key tyrosine residues, which serve as binding sites for a variety of adaptor proteins and enzymes. This leads to the activation of downstream signaling pathways including the PI3K-AKT and MAPK-ERK cascades, which regulate processes such as gene transcription, cell survival, proliferation, and differentiation. The differential outcomes of these signaling events depend largely on the dimerization context: homodimerization of ERBB4 is generally associated with growth-inhibitory and pro-apoptotic signals, while heterodimerization with EGFR or ERBB2 can promote proliferative and oncogenic pathways (qiu2008mechanismofactivation pages 7-8, wee2017epidermalgrowthfactor pages 20-22).

In addition to its conventional role as a plasma membrane receptor, regulated intramembrane proteolysis of ERBB4 can generate a soluble intracellular domain that translocates to the nucleus and may participate in direct transcriptional regulation. This dual signaling capacity allows ERBB4 to coordinate extracellular signals with genomic responses, thereby playing a multifunctional role in cellular homeostasis (OpenTargets Search: -ERBB4, wee2017epidermalgrowthfactor pages 22-24). The complexity of ERBB4 signaling is further underscored by the existence of multiple splice variants with distinct cytoplasmic domains that confer differential abilities to activate downstream pathways, a phenomenon that has been extensively documented in developmental and cancer research (OpenTargets Search: -ERBB4).

1. Other Comments  
   Several pharmacological agents have been investigated for their ability to modulate ERBB4 activity, although most inhibitors target multiple ErbB family members. For instance, small molecule tyrosine kinase inhibitors such as lapatinib and vandetanib have been shown to interact with the ATP-binding pocket of ErbB family receptors, including ERBB4, and have demonstrated efficacy in the treatment of certain cancers (wu2015fdaapprovedsmallmoleculekinase pages 30-34, noble2004proteinkinaseinhibitors pages 5-6). However, the efficacy and specificity of these agents toward ERBB4 are often influenced by the receptor’s dimerization state and the presence of disease-associated mutations.

Disease associations with ERBB4 are broad and include multiple cancer types such as breast cancer, colorectal cancer, lung adenocarcinoma, glioblastoma, and melanoma. Somatic mutations in ERBB4 have been reported, with gain-of-function mutations augmenting heterodimer-driven oncogenic signaling in several tumor types, while loss-of-function mutations, particularly in breast cancer, have been implicated in more aggressive phenotypes. In colorectal cancer, for example, approximately 7.5–11% of tumors harbor nonsynonymous mutations in ERBB4 and around 1.5% of these are predicted to be driver mutations (OpenTargets Search: -ERBB4, qiu2008mechanismofactivation pages 3-5). Post-translational regulation via ectodomain shedding by ADAM metalloproteinases also influences ERBB4 activity, further contributing to its role in disease pathogenesis (edwards2008theadammetalloproteinases pages 30-31, seals2003theadamsfamily pages 9-10). These associations underscore the importance of further research into ERBB4 as both a biomarker and potential therapeutic target in oncology.

1. References
2. OpenTargets Search: -ERBB4
3. qiu2008mechanismofactivation pages 1-2
4. qiu2008mechanismofactivation pages 3-5
5. qiu2008mechanismofactivation pages 6-7
6. qiu2008mechanismofactivation pages 7-8
7. wu2015fdaapprovedsmallmoleculekinase pages 30-34
8. edwards2008theadammetalloproteinases pages 30-31
9. harris2003egfreceptorligands pages 8-9
10. seals2003theadamsfamily pages 9-10
11. wee2017epidermalgrowthfactor pages 25-27
12. wu2015fdaapprovedsmallmoleculekinase pages 10-14
13. harris2003egfreceptorligands pages 11-12
14. harris2003egfreceptorligands pages 7-8
15. wee2017epidermalgrowthfactor pages 11-13
16. wee2017epidermalgrowthfactor pages 20-22
17. wee2017epidermalgrowthfactor pages 22-24
18. wee2017epidermalgrowthfactor pages 37-39
19. wee2017epidermalgrowthfactor pages 41-42
20. wee2017epidermalgrowthfactor pages 5-6
21. edwards2008theadammetalloproteinases pages 18-19
22. edwards2008theadammetalloproteinases pages 19-21
23. edwards2008theadammetalloproteinases pages 26-27
24. noble2004proteinkinaseinhibitors pages 5-6
25. wee2017epidermalgrowthfactor pages 10-11
26. wee2017epidermalgrowthfactor pages 22-24
27. wee2017epidermalgrowthfactor pages 24-25
28. wee2017epidermalgrowthfactor pages 3-5
29. wee2017epidermalgrowthfactor pages 30-32
30. wu2015fdaapprovedsmallmoleculekinase pages 1-6
31. edwards2008theadammetalloproteinases pages 29-30
32. edwards2008theadammetalloproteinases pages 33-33
33. hanada2004structureregulationand pages 9-11

References

1. (OpenTargets Search: -ERBB4): Open Targets Query (-ERBB4, 5 results). Buniello, A. et al. (2025). Open Targets Platform: facilitating therapeutic hypotheses building in drug discovery. Nucleic Acids Research.
2. (qiu2008mechanismofactivation pages 1-2): Chen Qiu, Mary K. Tarrant, Sung Hee Choi, Aruna Sathyamurthy, Ron Bose, Sudeep Banjade, Ashutosh Pal, William G. Bornmann, Mark A. Lemmon, Philip A. Cole, and Daniel J. Leahy. Mechanism of activation and inhibition of the her4/erbb4 kinase. Structure, 16:460-467, Mar 2008. URL: https://doi.org/10.1016/j.str.2007.12.016, doi:10.1016/j.str.2007.12.016. This article has 223 citations and is from a domain leading peer-reviewed journal.
3. (qiu2008mechanismofactivation pages 3-5): Chen Qiu, Mary K. Tarrant, Sung Hee Choi, Aruna Sathyamurthy, Ron Bose, Sudeep Banjade, Ashutosh Pal, William G. Bornmann, Mark A. Lemmon, Philip A. Cole, and Daniel J. Leahy. Mechanism of activation and inhibition of the her4/erbb4 kinase. Structure, 16:460-467, Mar 2008. URL: https://doi.org/10.1016/j.str.2007.12.016, doi:10.1016/j.str.2007.12.016. This article has 223 citations and is from a domain leading peer-reviewed journal.
4. (qiu2008mechanismofactivation pages 6-7): Chen Qiu, Mary K. Tarrant, Sung Hee Choi, Aruna Sathyamurthy, Ron Bose, Sudeep Banjade, Ashutosh Pal, William G. Bornmann, Mark A. Lemmon, Philip A. Cole, and Daniel J. Leahy. Mechanism of activation and inhibition of the her4/erbb4 kinase. Structure, 16:460-467, Mar 2008. URL: https://doi.org/10.1016/j.str.2007.12.016, doi:10.1016/j.str.2007.12.016. This article has 223 citations and is from a domain leading peer-reviewed journal.
5. (qiu2008mechanismofactivation pages 7-8): Chen Qiu, Mary K. Tarrant, Sung Hee Choi, Aruna Sathyamurthy, Ron Bose, Sudeep Banjade, Ashutosh Pal, William G. Bornmann, Mark A. Lemmon, Philip A. Cole, and Daniel J. Leahy. Mechanism of activation and inhibition of the her4/erbb4 kinase. Structure, 16:460-467, Mar 2008. URL: https://doi.org/10.1016/j.str.2007.12.016, doi:10.1016/j.str.2007.12.016. This article has 223 citations and is from a domain leading peer-reviewed journal.
6. (wu2015fdaapprovedsmallmoleculekinase pages 30-34): Peng Wu, Thomas E. Nielsen, and Mads H. Clausen. Fda-approved small-molecule kinase inhibitors. Trends in Pharmacological Sciences, 36:422-439, Jul 2015. URL: https://doi.org/10.1016/j.tips.2015.04.005, doi:10.1016/j.tips.2015.04.005. This article has 1168 citations and is from a highest quality peer-reviewed journal.
7. (edwards2008theadammetalloproteinases pages 30-31): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
8. (harris2003egfreceptorligands pages 8-9): RC Harris. Egf receptor ligands. Unknown journal, 2003.
9. (qiu2008mechanismofactivation pages 5-6): Chen Qiu, Mary K. Tarrant, Sung Hee Choi, Aruna Sathyamurthy, Ron Bose, Sudeep Banjade, Ashutosh Pal, William G. Bornmann, Mark A. Lemmon, Philip A. Cole, and Daniel J. Leahy. Mechanism of activation and inhibition of the her4/erbb4 kinase. Structure, 16:460-467, Mar 2008. URL: https://doi.org/10.1016/j.str.2007.12.016, doi:10.1016/j.str.2007.12.016. This article has 223 citations and is from a domain leading peer-reviewed journal.
10. (seals2003theadamsfamily pages 9-10): Darren F. Seals and Sara A. Courtneidge. The adams family of metalloproteases: multidomain proteins with multiple functions. Genes & Development, 17:7-30, Jan 2003. URL: https://doi.org/10.1101/gad.1039703, doi:10.1101/gad.1039703. This article has 1569 citations.
11. (wee2017epidermalgrowthfactor pages 25-27): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
12. (wu2015fdaapprovedsmallmoleculekinase pages 10-14): Peng Wu, Thomas E. Nielsen, and Mads H. Clausen. Fda-approved small-molecule kinase inhibitors. Trends in Pharmacological Sciences, 36:422-439, Jul 2015. URL: https://doi.org/10.1016/j.tips.2015.04.005, doi:10.1016/j.tips.2015.04.005. This article has 1168 citations and is from a highest quality peer-reviewed journal.
13. (harris2003egfreceptorligands pages 11-12): RC Harris. Egf receptor ligands. Unknown journal, 2003.
14. (harris2003egfreceptorligands pages 7-8): RC Harris. Egf receptor ligands. Unknown journal, 2003.
15. (wee2017epidermalgrowthfactor pages 11-13): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
16. (wee2017epidermalgrowthfactor pages 20-22): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
17. (wee2017epidermalgrowthfactor pages 22-24): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
18. (wee2017epidermalgrowthfactor pages 37-39): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
19. (wee2017epidermalgrowthfactor pages 41-42): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
20. (wee2017epidermalgrowthfactor pages 5-6): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
21. (edwards2008theadammetalloproteinases pages 18-19): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
22. (edwards2008theadammetalloproteinases pages 19-21): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
23. (edwards2008theadammetalloproteinases pages 26-27): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
24. (noble2004proteinkinaseinhibitors pages 5-6): Martin E. M. Noble, Jane A. Endicott, and Louise N. Johnson. Protein kinase inhibitors: insights into drug design from structure. Science, 303:1800-1805, Mar 2004. URL: https://doi.org/10.1126/science.1095920, doi:10.1126/science.1095920. This article has 1725 citations and is from a highest quality peer-reviewed journal.
25. (wee2017epidermalgrowthfactor pages 10-11): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
26. (wee2017epidermalgrowthfactor pages 24-25): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
27. (wee2017epidermalgrowthfactor pages 3-5): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
28. (wee2017epidermalgrowthfactor pages 30-32): Ping Wee and Zhixiang Wang. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers, 9:52, May 2017. URL: https://doi.org/10.3390/cancers9050052, doi:10.3390/cancers9050052. This article has 2089 citations and is from a peer-reviewed journal.
29. (wu2015fdaapprovedsmallmoleculekinase pages 1-6): Peng Wu, Thomas E. Nielsen, and Mads H. Clausen. Fda-approved small-molecule kinase inhibitors. Trends in Pharmacological Sciences, 36:422-439, Jul 2015. URL: https://doi.org/10.1016/j.tips.2015.04.005, doi:10.1016/j.tips.2015.04.005. This article has 1168 citations and is from a highest quality peer-reviewed journal.
30. (edwards2008theadammetalloproteinases pages 29-30): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
31. (edwards2008theadammetalloproteinases pages 33-33): D. Edwards, M. Handsley, and C. Pennington. The adam metalloproteinases. Molecular Aspects of Medicine, 29:258-289, Oct 2008. URL: https://doi.org/10.1016/j.mam.2008.08.001, doi:10.1016/j.mam.2008.08.001. This article has 1623 citations and is from a highest quality peer-reviewed journal.
32. (hanada2004structureregulationand pages 9-11): Masahito Hanada, Jianhua Feng, and Brian A Hemmings. Structure, regulation and function of pkb/akt—a major therapeutic target. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1697:3-16, Mar 2004. URL: https://doi.org/10.1016/j.bbapap.2003.11.009, doi:10.1016/j.bbapap.2003.11.009. This article has 1100 citations.