

References

- Bahar, M. E., Kim, H. J., & Kim, D. R. (2023). Targeting the RAS/RAF/MAPK pathway for cancer therapy: From mechanism to clinical studies. *Signal Transduction and Targeted Therapy*, 8(1). <https://doi.org/10.1038/s41392-023-01705-z>
- Bai, X., Sun, P., Wang, X., Long, C., Liao, S., Dang, S., Zhuang, S., Du, Y., Zhang, X., Li, N., He, K., & Zhang, Z. (2023). Structure and dynamics of the EGFR/HER2 heterodimer. *Cell Discovery*, 9(1). <https://doi.org/10.1038/s41421-023-00523-5>
- Barros, F., Powe, D. G., Ellis, I. O., & Green, A. (2010). Understanding the HER family in breast cancer: Interaction with ligands, dimerization and treatments. *Histopathology*, 56(5), 560–572. <https://doi.org/10.1111/j.1365-2559.2010.03494.x>
- Best, R. L., LaPointe, N. E., Azarenko, O., Miller, H., Genualdi, C., Chih, S., Shen, B.-Q., Jordan, M. A., Wilson, L., Feinstein, S. C., & Stagg, N. J. (2021). Microtubule and tubulin binding and regulation of microtubule dynamics by the antibody drug conjugate (ADC) payload, monomethyl auristatin E (MMAE): Mechanistic insights into MMAE ADC peripheral neuropathy. *Toxicology and Applied Pharmacology*, 421, 115534. <https://doi.org/10.1016/j.taap.2021.115534>
- Bhakta-Yadav, M. S., & Brown, T. L. (2025). Important aspects of siRNA design for optimal efficacy in vitro and in vivo. *International Journal of Cell Biology*, 2025(1). <https://doi.org/10.1155/ijcb/6663816>
- Cai, X., Zhang, L., & Chen, S. (2022). Editorial: Cancer treatment and early detection targeting HER receptors. *Frontiers in Molecular Biosciences*, 9. <https://doi.org/10.3389/fmolb.2022.940055>
- Chen, W., Gupta, A., Mai, N., Nag, S., Lau, J. S., Singh, S., Chodera, J. D., Liu, B., de Stanchina, E., Pareja, F., Hashmi, A. Ali., Lieberman, M. M., Modi, S., Bromberg, J., Razavi, P., Drago, J. Z., & Chandarlapaty, S. (2025). Trastuzumab deruxtecan (t-dxd) resistance via loss of HER2 expression and binding. *Cancer Discovery*. <https://doi.org/10.1158/2159-8290.cd-25-0647>

- Cheng, X. (2024). A comprehensive review of HER2 in cancer biology and therapeutics. *Genes*, 15(7), 903–903. <https://doi.org/10.3390/genes15070903>
- Chiang, W. F., Cheng, T. M., Chang, C. C., Pan, S. H., Changou, C. A., Chang, T. H., Lee, K. H., Wu, S. Y., Chen, Y. F., Chuang, K. H., Shieh, D. B., Chen, Y. L., Tu, C. C., Tsui, W. L., & Wu, M. H. (2018). Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) promotes EGF receptor signaling of oral squamous cell carcinoma metastasis via the complex N-glycosylation. *Oncogene*, 37(1), 116–127. <https://doi.org/10.1038/onc.2017.303>
- Ćorović, M., Hoch-Kraft, P., Zhou, Y., Hallstein, S., König, J., & Zarnack, K. (2025). M6A in the coding sequence: Linking deposition, translation, and decay. *Trends in Genetics*, 41(11), 963–973. <https://doi.org/10.1016/j.tig.2025.06.002>
- Cretella, D., Saccani, F., Quaini, F., Frati, C., Lagrasta, C., Bonelli, M., Caffarra, C., Cavazzoni, A., Fumarola, C., Galetti, M., La Monica, S., Ampollini, L., Tiseo, M., Ardizzoni, A., Petronini, P. G., & Alfieri, R. R. (2014). Trastuzumab emtansine is active on HER-2 overexpressing NSCLC cell lines and overcomes gefitinib resistance. *Molecular Cancer*, 13(1). <https://doi.org/10.1186/1476-4598-13-143>
- El-Gamal, M. I., Mewafi, N. H., Abdelmotteleb, N. E., Emara, M. A., Tarazi, H., Sbenati, R. M., Madkour, M. M., Zariaei, S.-O., Shahin, A. I., & Anbar, H. S. (2021). A review of HER4 (erbb4) kinase, its impact on cancer, and its inhibitors. *Molecules*, 26(23), 7376. <https://doi.org/10.3390/molecules26237376>
- European Medicines Agency. (2025). *Enhertu (trastuzumab deruxtecan)*. https://www.ema.europa.eu/en/documents/overview/enhertu-epar-medicine-overview_en.pdf
- Ferguson, K. M. (2008). Structure-Based view of epidermal growth factor receptor regulation. *Annual Review of Biophysics*, 37(1), 353–373. <https://doi.org/10.1146/annurev.biophys.37.032807.125829>

- Fuchs, A., Riegler, S., Ayatollahi, Z., Cavallari, N., Giono, L. E., Nimeth, B. A., Mutanwad, K. V., Schweighofer, A., Lucyshyn, D., Barta, A., Petrillo, E., & Kalyna, M. (2021). Targeting alternative splicing by RNAi: From the differential impact on splice variants to triggering artificial pre-mRNA splicing. *Nucleic Acids Research*, 49(2), 1133–1151. <https://doi.org/10.1093/nar/gkaa1260>
- Galogre, M. I., Rodin, D., Pyatnitskiy, M. A., Mackelprang, M., & Koman, I. (2023). A review of HER2 overexpression and somatic mutations in cancers. *Critical Reviews in Oncology/Hematology*, 186, 103997–103997. <https://doi.org/10.1016/j.critrevonc.2023.103997>
- Gogia, P., Ashraf, H., Bhasin, S., & Xu, Y. (2023). Antibody–Drug conjugates: A review of approved drugs and their clinical level of evidence. *Cancers*, 15(15), 3886–3886. <https://doi.org/10.3390/cancers15153886>
- Greenblatt, K., & Khaddour, K. (2020). *Trastuzumab*. PubMed; StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK532246/>
- He, J., Zeng, X., Wang, C., Wang, E., & Li, Y. (2024). Antibody-drug conjugates in cancer therapy: Mechanisms and clinical studies. *MedComm*, 5(8), e671. <https://doi.org/10.1002/mco2.671>
- He, Y., Sun, M. M., Zhang, G. G., Yang, J., Chen, K. S., Xu, W. W., & Li, B. (2021). Targeting PI3K/AKT signal transduction for cancer therapy. *Signal Transduction and Targeted Therapy*, 6(1), 1–17. <https://doi.org/10.1038/s41392-021-00828-5>
- Hsu, J. L., & Hung, M.-C. (2016). The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer. *Cancer and Metastasis Reviews*, 35(4), 575–588. <https://doi.org/10.1007/s10555-016-9649-6>
- Johnson, B., & Mahadevan, D. (2015). Emerging role and targeting of carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) in human malignancies. *Clinical Cancer Drugs*, 2(2), 100–111. <https://doi.org/10.2174/2212697x02666150602215823>

- Kennedy, S. P., Hastings, J. F., Han, J. Z. R., & Croucher, D. R. (2016). The under-appreciated promiscuity of the epidermal growth factor receptor family. *Frontiers in Cell and Developmental Biology*, 4. <https://doi.org/10.3389/fcell.2016.00088>
- Kim, E. Y., Cha, Y. J., Jeong, S., & Chang, Y. S. (2022). Overexpression of CEACAM6 activates src-fak signaling and inhibits anoikis, through homophilic interactions in lung adenocarcinomas. *Translational Oncology*, 20, 101402. <https://doi.org/10.1016/j.tranon.2022.101402>
- Kim, S. H., Park, Y., Min, A., Park, H. Y., Kim, Y.-J., Ham, S., Koh, J., Kim, S., Lee, D.-W., Ryu, H. S., Kim, J.-S., Lee, K.-H., & Im, S.-A. (2026). DNA damage and nuclear anaplasia induced by trastuzumab deruxtecan in cancer cells with variable HER2 expression and homologous recombination deficiency status. *Cancer Research and Treatment*, 58(2), 407–422. <https://doi.org/10.4143/crt.2025.201>
- Luque-Cabal, M., García-Tejido, P., Fernández-Pérez, Y., Sánchez-Lorenzo, L., & Palacio-Vázquez, I. (2016). Mechanisms behind the resistance to trastuzumab in her2-amplified breast cancer and strategies to overcome it. *Clinical Medicine Insights: Oncology*, 10s1, CMO.S34537. <https://doi.org/10.4137/cmo.s34537>
- Lyu, H., Han, A., Polsdofer, E., Liu, S., & Liu, B. (2018). Understanding the biology of HER3 receptor as a therapeutic target in human cancer. *Acta Pharmaceutica Sinica B*, 8(4), 503–510. <https://doi.org/10.1016/j.apsb.2018.05.010>
- Maadi, H., Soheilifar, M. H., Choi, W.-S., Moshtaghian, A., & Wang, Z. (2021). Trastuzumab mechanism of action; 20 years of research to unravel a dilemma. *Cancers*, 13(14), 3540. <https://doi.org/10.3390/cancers13143540>
- Mashayekh-Poul, R., Azimzadeh-Irani, M., & Masoomi-Nomandan, S. Z. (2023). Structural arrangement of the active back-to-back dimer in N-glycosylated ErbB receptors is regulated by heterodimerization. *Molecular Biology Research Communications*, 12(3), 95–107. <https://doi.org/10.22099/mbrc.2023.47147.1822>

- Mercogliano, M. F., De Martino, M., Venturutti, L., Rivas, M. A., Proietti, C. J., Inurrigarro, G., Frahm, I., Allemand, D. H., Deza, E. G., Ares, S., Gercovich, F. G., Guzmán, P., Roa, J. C., Elizalde, P. V., & Schillaci, R. (2016). TNF α -Induced mucin 4 expression elicits trastuzumab resistance in her2-positive breast cancer. *Clinical Cancer Research*, 23(3), 636–648. <https://doi.org/10.1158/1078-0432.ccr-16-0970>
- Miao, Y., Du, Q., Zhang, H., Yuan, Y., Zuo, Y., & Zheng, H. (2023). Cycloheximide (CHX) chase assay to examine protein half-life. *Bio-Protocol*, 13(11). <https://doi.org/10.21769/bioprotoc.4690>
- Ouyang, Q., Tian, C., Gao, J., Huang, J., Fu, H., He, J., & Yang, J. (2016). HER2-positive double primary tumor of gastric and breast cancer occur synchronously in a patient: A case report. *Molecular and Clinical Oncology*, 4(5), 719–722. <https://doi.org/10.3892/mco.2016.812>
- Pan, L., Li, J., Xu, Q., Gao, Z., Yang, M., Wu, X., & Li, X. (2024). HER2/PI3K/AKT pathway in HER2-positive breast cancer: A review. *Medicine*, 103(24), e38508–e38508. <https://doi.org/10.1097/md.00000000000038508>
- Park, M.-Y., Jung, M. H., Eo, E. Y., Kim, S., Lee, S. H., Lee, Y. J., Park, J. S., Cho, Y. J., Chung, J. H., Kim, C. H., Yoon, H. I., Lee, J. H., & Lee, C.-T. (2017). Generation of lung cancer cell lines harboring EGFR T790M mutation by CRISPR/Cas9-mediated genome editing. *Oncotarget*, 8(22). <https://doi.org/10.18632/oncotarget.16752>
- Popović, L., Wintgens, J. P., Wu, Y., Brankatschk, B., Menninger, S., Degenhart, C., Jensen, N., Wichert, S. P., Klebl, B., Rossner, M. J., & Wehr, M. C. (2024). Profiling of ERBB receptors and downstream pathways reveals selectivity and hidden properties of ERBB4 antagonists. *IScience*, 27(2), 108839–108839. <https://doi.org/10.1016/j.isci.2024.108839>
- Roskoski, R. (2014). The ErbB/HER family of protein-tyrosine kinases and cancer. *Pharmacological Research*, 79, 34–74. <https://doi.org/10.1016/j.phrs.2013.11.002>
- Sassen, A., Rochon, J., Wild, P., Hartmann, A., Hofstaedter, F., Schwarz, S., & Brockhoff, G. (2008). Cytogenetic analysis of HER1/EGFR, HER2, HER3 and HER4 in 278 breast cancer patients. *Breast Cancer Research*, 10(1). <https://doi.org/10.1186/bcr1843>

- Sledge, G. W., Xiu, J., Mahtani, R. L., Sandoval, A. C., Meric-Bernstam, F., Ribeiro, J. R., Kulkarni, N. N., Rampa, D. R., Lee, J., Ueno, N. T., Oberley, M. J., Radovich, M., & Spetzler, D. B. (2025). Mechanisms of resistance to trastuzumab deruxtecan in breast cancer elucidated by multi-omic molecular profiling. *Npj Breast Cancer*, 12(1), 1–1. <https://doi.org/10.1038/s41523-025-00868-y>
- Swain, S. M., Shastry, M., & Hamilton, E. (2022). Targeting her2-positive breast cancer: Advances and future directions. *Nature Reviews Drug Discovery*, 22(2), 1–26.
- Topalan, E., Büyükgüngör, A., Çiğdem, M., Güra, S., Sever, B., Otsuka, M., Fujita, M., Demirci, H., & Ciftci, H. (2025). A structural insight into two important erbb receptors (EGFR and HER2) and their relevance to non-small cell lung cancer. *Archiv Der Pharmazie*, 358(4). <https://doi.org/10.1002/ardp.202400992>
- Vu, T., & Claret, F. X. (2012). Trastuzumab: Updated mechanisms of action and resistance in breast cancer. *Frontiers in Oncology*, 2(62). <https://doi.org/10.3389/fonc.2012.00062>
- Waight, A. B., Bargsten, K., Doronina, S., Steinmetz, M. O., Sussman, D., & Protá, A. E. (2016). Structural basis of microtubule destabilization by potent auristatin anti-mitotics. *PLoS ONE*, 11(8), e0160890. <https://doi.org/10.1371/journal.pone.0160890>
- Wang, L., Wang, Y., Li, Y., Zhou, L., Du, J., Wang, J., Liu, S., Cao, Y., Li, Y., Yang, W., & Zhu, T. (2024). Resistance mechanisms and prospects of trastuzumab. *Frontiers in Oncology*, 14. <https://doi.org/10.3389/fonc.2024.1389390>
- Wang, Y., Cheng, X., Li, X., Chen, W., Zhang, X., & Liu, Y. (2025). Bystander effect in antibody-drug conjugates: Navigating the fine line in tumor heterogeneity. *Critical Reviews in Oncology/Hematology*, 216, 104979. <https://doi.org/10.1016/j.critrevonc.2025.104979>
- Xie, H., Wang, X., Zhang, P., Li, Q., & Chen, J. (2026). Innovations in HER2-targeted therapy: A comprehensive review of trastuzumab deruxtecan. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1881(2), 189550. <https://doi.org/10.1016/j.bbcan.2026.189550>

- Xu, X.-M., Yoo, M.-H., Carlson, B. A., Gladyshev, V. N., & Hatfield, D. L. (2009). Simultaneous knockdown of the expression of two genes using multiple shRNAs and subsequent knock-in of their expression. *Nature Protocols*, 4(9), 1338–1348. <https://doi.org/10.1038/nprot.2009.145>
- Yan, M., Schwaederle, M., Arguello, D., Millis, S. Z., Gatalica, Z., & Kurzrock, R. (2015). HER2 expression status in diverse cancers: review of results from 37,992 patients. *Cancer Metastasis Reviews*, 34, 157–164. <https://doi.org/10.1007/s10555-015-9552-6>
- Zhao, X., Li, Y., Zhang, H., Cai, Y., Wang, X., Liu, Y., Li, T., Xu, C., Teng, Y., Li, D., & Li, F. (2025). PAK5 promotes the trastuzumab resistance by increasing HER2 nuclear accumulation in HER2-positive breast cancer. *Cell Death and Disease*, 16(1). <https://doi.org/10.1038/s41419-025-07657-2>
- Zheng, M.-Y., Lin, Y.-T., Kuo, Y.-S., Lin, Y.-J., Kuo, M.-H., Huang, T.-W., Shieh, Y.-S., Huang, Y., & Chou, Y.-T. (2025). Cytokine and epigenetic regulation of CEACAM6 mediates EGFR-driven signaling and drug response in lung adenocarcinoma. *Npj Precision Oncology*, 9(1). <https://doi.org/10.1038/s41698-025-00910-z>
- Zhu, M., Yu, M., Meng, Y., Yang, J., Wang, X., Li, L., Liang, Y., & Kong, F. (2024). HER3 receptor and its role in the therapeutic management of metastatic breast cancer. *Journal of Translational Medicine*, 22(1). <https://doi.org/10.1186/s12967-024-05445-8>