

## REFERENCES

- Alexander, P.B., Chen, R., Gong, C., Yuan, L., Jasper, J.S., Ding, Y., Markowitz, G.J., Yang, P., Xu, X., McDonnell, D.P., Song, E., Wang, X.-F., 2017. Distinct Receptor Tyrosine Kinase Subsets Mediate Anti-HER2 Drug Resistance in Breast Cancer\*. *J. Biol. Chem.* 292, 748–759.
- Ali, Z., Hermawan, A., 2022. Bioinformatics Analysis Uncovers the Importance of RTK-RAS-PI3K/Akt Regulation by Borneol in Overcoming Breast Cancer Resistance to Tamoxifen. *Indones. J. Pharm.* 33, 135–146.
- Alt, J.R., Cleveland, J.L., Hannink, M., Diehl, J.A., 2000. Phosphorylation-dependent regulation of cyclin D1 nuclear export and cyclin D1-dependent cellular transformation. *Genes Dev.* 14, 3102–3114.
- Arnold, M., Morgan, E., Rungay, H., Mafra, A., Singh, D., Laversanne, M., Vignat, J., Gralow, J.R., Cardoso, F., Siesling, S., Soerjomataram, I., 2022. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast* 66, 15–23.
- Arya, M., Shergill, I.S., Williamson, M., Gommersall, L., Arya, N., Patel, H.R.H., 2005. Basic principles of real-time quantitative PCR. *Expert Rev. Mol. Diagn.* 5, 209–219.
- Askari, B.S., Krajinovic, M., 2010. Dihydrofolate reductase gene variations in susceptibility to disease and treatment outcomes. *Curr. Genomics* 11, 578–583.
- Ateeq, B., Tomlins, S.A., Chinnaiyan, A.M., 2009. AGTR1 as a therapeutic target in ER-positive and ERBB2-negative breast cancer cases. *Cell Cycle* 8, 3794–3795.
- Bayat, A., 2002. Clinical review Science, medicine, and the future Bioinformatics. *Bmj* 324, 1018–22.
- Breslin, S., O’Driscoll, L., 2016. The relevance of using 3D cell cultures, in addition to 2D monolayer cultures, when evaluating breast cancer drug sensitivity and resistance. *Oncotarget* 7, 45745–45756.
- Burguin, A., Diorio, C., Durocher, F., 2021. Breast cancer treatments: Updates and new challenges. *J. Pers. Med.* 11.
- Canfield, K., Li, J., Wilkins, O.M., Morrison, M.M., Ung, M., Wells, W., Williams, C.R., Liby, K.T., Vullhorst, D., Buonanno, A., Hu, H., Schiff, R., Cook, R.S., Kurokawa, M., 2015. Receptor tyrosine kinase ERBB4 mediates acquired resistance to ERBB2 inhibitors in breast cancer cells. *Cell Cycle* 14, 648–655.
- Cao, W., Li, Y., Hou, Y., Yang, M., Fu, X., Zhao, B., 2019. Biomedicine & Pharmacotherapy Enhanced anticancer efficiency of doxorubicin against human glioma by natural borneol through triggering ROS-mediated signal.

Biomed. Pharmacother. 118, 109261.

- Cao, W. qiang, Li, Y., Hou, Y. jun, Yang, M. xun, Fu, Xue qi, Zhao, B. song, Jiang, H. ming, Fu, Xiao yan, 2019. Enhanced anticancer efficiency of doxorubicin against human glioma by natural borneol through triggering ROS-mediated signal. *Biomed. Pharmacother.* 118, 109261.
- Chen, J., Li, L., Su, J., Chen, T., 2015. Natural borneol enhances bisdemethoxycurcumin-induced cell cycle arrest in the G2/M phase through up-regulation of intracellular ROS in HepG2 cells. *Food Funct.* 6, 740–748.
- Chen, Y., Lu, A., Hu, Z., Li, J., Lu, J., 2024. ERBB3 targeting: A promising approach to overcoming cancer therapeutic resistance. *Cancer Lett.* 599, 217146.
- Chou, T.-C., 2010. Drug combination studies and their synergy quantification using the Chou-Talalay method. *Cancer Res.* 70, 440–446.
- Coqueret, O., 2003. New roles for p21 and p27 cell-cycle inhibitors: a function for each cell compartment? *Trends Cell Biol.* 13, 65–70.
- Coulson, R.S., Deb, S., Ernst, M., Allen, A., Chand, A.L., 2016. Abstract LB-257: The angiotensin receptor blocker, Losartan, inhibits mammary tumor development and progression to invasive carcinoma. *Cancer Res.* 76, LB-257-LB-257.
- D'Amato, V., Raimondo, L., Formisano, L., Giuliano, M., De Placido, S., Rosa, R., Bianco, R., 2015. Mechanisms of lapatinib resistance in HER2-driven breast cancer. *Cancer Treat. Rev.* 41, 877–883.
- de Abreu Pereira, D., Sandim, V., Fernandes, T.F.B., Almeida, V.H., Rocha, M.R., do Amaral, R.J.F.C., Rossi, M.I.D., Kalume, D.E., Zingali, R.B., 2022. Proteomic Analysis of HCC-1954 and MCF-7 Cell Lines Highlights Crosstalk between  $\alpha v$  and  $\beta 1$  Integrins, E-Cadherin and HER-2. *Int. J. Mol. Sci.*
- Diaz, R., Nguewa, P., Parrondo, R., Perez-Stable, C., Manrique, I., Redrado, M., Catena, R., Collantes, M., Penuelas, I., Díaz-González, J., Calvo, A., 2010. Antitumor and antiangiogenic effect of the dual EGFR and HER-2 tyrosine kinase inhibitor lapatinib in a lung cancer model. *BMC Cancer* 10, 188.
- Dieckman, L.M., Freudenthal, B.D., Washington, M.T., 2012. PCNA structure and function: insights from structures of PCNA complexes and post-translationally modified PCNA. *Subcell. Biochem.* 62, 281–299.
- Domené, S., Scaglia, P.A., Gutiérrez, M.L., Domené, H.M., 2021. Applying bioinformatic platforms, in vitro, and in vivo functional assays in the characterization of genetic variants in the GH/IGF pathway affecting growth and development. *Cells* 10.
- Dong, C., Wu, J., Chen, Y., Nie, J., Chen, C., 2021. Activation of PI3K/AKT/mTOR Pathway Causes Drug Resistance in Breast Cancer. *Front. Pharmacol.* 12, 1–16.

- Dong, P., Gewirtz, D.A., 2022. Editorial: Risks and Benefits of Adjuvants to Cancer Therapies. *Front. Oncol.* 12, 10–12.
- Eliyatkin, N., Yalcin, E., Zengel, B., Aktaş, S., Vardar, E., 2015. Molecular Classification of Breast Carcinoma: From Traditional, Old-Fashioned Way to A New Age, and A New Way. *J. Breast Heal.* 11, 59–66.
- Eustace, Alex J., Conlon, N.T., McDermott, M.S.J., Browne, B.C., O’Leary, P., Holmes, F.A., Espina, V., Liotta, L.A., O’Shaughnessy, J., Gallagher, C., O’Driscoll, L., Rani, S., Madden, S.F., O’Brien, N.A., Ginther, C., Slamon, D., Walsh, N., Gallagher, W.M., Zagazdzon, R., Watson, W.R., O’Donovan, N., Crown, J., 2018. Development of acquired resistance to lapatinib may sensitise HER2-positive breast cancer cells to apoptosis induction by obatoclax and TRAIL. *BMC Cancer* 18, 1–14.
- Eustace, Alex J., Conlon, N.T., McDermott, M.S.J., Browne, B.C., O’Leary, P., Holmes, F.A., Espina, V., Liotta, L.A., O’Shaughnessy, J., Gallagher, C., O’Driscoll, L., Rani, S., Madden, S.F., O’Brien, N.A., Ginther, C., Slamon, D., Walsh, N., Gallagher, W.M., Zagazdzon, R., Watson, W.R., O’Donovan, N., Crown, J., 2018. Development of acquired resistance to lapatinib may sensitise HER2-positive breast cancer cells to apoptosis induction by obatoclax and TRAIL. *BMC Cancer* 18, 965.
- Farrugia, M.K., Sharma, S.B., Lin, C.C., McLaughlin, S.L., Vanderbilt, D.B., Ammer, A.G., Salkeni, M.A., Stoilov, P., Agazie, Y.M., Creighton, C.J., Ruppert, J.M., 2015. Regulation of anti-apoptotic signaling by Kruppel-like factors 4 and 5 mediates lapatinib resistance in breast cancer. *Cell Death Dis.* 6, 1–12.
- Fritsch, M., Günther, S.D., Schwarzer, R., Albert, M.-C., Schorn, F., Werthenbach, J.P., Schiffmann, L.M., Stair, N., Stocks, H., Seeger, J.M., Lamkanfi, M., Krönke, M., Pasparakis, M., Kashkar, H., 2019. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. *Nature* 575, 683–687.
- Fujimoto, Y., Morita, T.Y., Ohashi, A., Haeno, H., Hakozaiki, Y., Fujii, M., Kashima, Y., Kobayashi, S.S., Mukohara, T., 2020. Combination treatment with a PI3K/Akt/mTOR pathway inhibitor overcomes resistance to anti-HER2 therapy in PIK3CA-mutant HER2-positive breast cancer cells. *Sci. Rep.* 10, 1–16.
- Gallo, S., Vitacolonna, A., Comoglio, P., Crepaldi, T., 2022. MET Oncogene Controls Invasive Growth by Coupling with NMDA Receptor 1–13.
- Garrett, J.T., Olivares, M.G., Rinehart, C., Granja-Ingram, N.D., Sánchez, V., Chakrabarty, A., Dave, B., Cook, R.S., Pao, W., McKinely, E., Manning, H.C., Chang, J., Arteaga, C.L., 2011. Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase. *Proc. Natl. Acad. Sci. U. S. A.* 108, 5021–5026.
- Gaulton, A., Bellis, L.J., Bento, A.P., Chambers, J., Davies, M., Hersey, A., Light, Y., McGlinchey, S., Michalovich, D., Al-Lazikani, B., Overington, J.P., 2012.

- ChEMBL: A large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* 40, 1100–1107.
- Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., Zoete, V., 2014. SwissTargetPrediction: A web server for target prediction of bioactive small molecules. *Nucleic Acids Res.* 42, 32–38.
- Ghasemi, M., Turnbull, T., Sebastian, S., Kempson, I., 2021. The mtt assay: Utility, limitations, pitfalls, and interpretation in bulk and single-cell analysis. *Int. J. Mol. Sci.* 22.
- Gilson, M.K., Liu, T., Baitaluk, M., Nicola, G., Hwang, L., Chong, J., 2016. BindingDB in 2015: A public database for medicinal chemistry, computational chemistry and systems pharmacology. *Nucleic Acids Res.* 44, D1045–D1053.
- Gimple, R.C., Wang, X., 2019. RAS: Striking at the Core of the Oncogenic Circuitry. *Front. Oncol.* 9, 1–16.
- Goel, S., DeCristo, M.J., McAllister, S.S., Zhao, J.J., 2018. CDK4/6 Inhibition in Cancer: Beyond Cell Cycle Arrest. *Trends Cell Biol.* 28, 911–925.
- Goel, S., Wang, Q., Watt, A.C., Tolaney, S.M., Dillon, D.A., Li, W., Ramm, S., Palmer, A.C., Yuzugullu, H., Varadan, V., Tuck, D., Harris, L.N., Wong, K.-K., Liu, X.S., Sicinski, P., Winer, E.P., Krop, I.E., Zhao, J.J., 2016. Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. *Cancer Cell* 29, 255–269.
- Gutierrez, C., Schiff, R., 2011. HER2: Biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 135, 55–62.
- Gyórfy, B., 2024. Integrated analysis of public datasets for the discovery and validation of survival-associated genes in solid tumors. *Innov.* 5.
- Han, H., Yang, S., Lin, S.G., Xu, C. Sen, Han, Z.H., 2014. Effects and mechanism of downregulation of COX-2 expression by RNA interference on proliferation and apoptosis of human breast cancer MCF-7 cells. *Mol. Med. Rep.* 10, 3092–3098.
- Hariono, M., Rollando, R., Karamoy, J., Hariyono, P., Atmono, M., Djohan, M., Wiwy, W., Nuwarda, R., Kurniawan, C., Salin, N., Wahab, H., 2020. Bioguided fractionation of local plants against matrix metalloproteinase9 and its cytotoxicity against breast cancer cell models: In silico and in vitro study. *Molecules* 25, 1–17.
- Heidegger, I., Fotakis, G., Offermann, A., Goveia, J., Daum, S., Salcher, S., Noureen, A., Timmer-Bosscha, H., Schäfer, G., Walenkamp, A., Perner, S., Beatovic, A., Moisse, M., Plattner, C., Krogsdam, A., Haybaeck, J., Sopper, S., Thaler, S., Keller, M.A., Klocker, H., Trajanoski, Z., Wolf, D., Pircher, A., 2022. Comprehensive characterization of the prostate tumor microenvironment identifies CXCR4/CXCL12 crosstalk as a novel antiangiogenic therapeutic target in prostate cancer. *Mol. Cancer* 21, 1–20.
- Hermawan, A., Ikawati, M., Khumaira, A., Putri, H., Jenie, R.I., Angraini, S.M.,

- Muflikhasari, H.A., 2021. Bioinformatics and in vitro studies reveal the importance of p53, PPAR $\gamma$  and notch signaling pathway in inhibition of breast cancer stem cells by hesperetin. *Adv. Pharm. Bull.* 11, 351–360.
- Hermawan, A., Putri, H., Hanif, N., Fatimah, N., Prasetyo, H.H., 2022. Identification of potential target genes of honokiol in overcoming breast cancer resistance to tamoxifen. *Front. Oncol.* 12, 1–18.
- Hermawan, A., Satria, D., Anjelisa, P., Hasibuan, Z., Huda, F., Syaury, A., Fatimah, N., Dewi, D., Putri, P., 2024. South African Journal of Botany Identification of potential target genes of cardiac glycosides from *Vernonia amygdalina* Delile in HER2 + breast cancer cells. *South African J. Bot.* 164, 401–418.
- Hermawan, A., Windarsih, A., Putri, D.D.P., Fatimah, N., 2025. LC-HRMS-based global metabolomics profiling unravels the distinct metabolic signature of lapatinib-resistant and trastuzumab-resistant HER2+ breast cancer cells. *J. Pharm. Biomed. Anal.* 253, 116528.
- Hsia, T.-C., Tu, C.-Y., Chen, Y.-J., Wei, Y.-L., Yu, M.-C., Hsu, S.-C., Tsai, S.-L., Chen, W.-S., Yeh, M.-H., Yen, C.-J., Yu, Y.-L., Huang, T.-C., Huang, C.-Y., Hung, M.-C., Huang, W.-C., 2013. Lapatinib-mediated cyclooxygenase-2 expression via epidermal growth factor receptor/HuR interaction enhances the aggressiveness of triple-negative breast cancer cells. *Mol. Pharmacol.* 83, 857–869.
- Huynh, T.K., Huang, C.H., Chen, J.Y., Yao, J.H., Yang, Y.S., Wei, Y.L., Chen, H.F., Chen, C.H., Tu, C.Y., Hsu, Y.M., Liu, L.C., Huang, W.C., 2021. miR-221 confers lapatinib resistance by negatively regulating p27kip1 in HER2-positive breast cancer. *Cancer Sci.* 112, 4234–4245.
- Iqbal, Nida, Iqbal, Naveed, 2014. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol. Biol. Int.* 2014, 1–9.
- Ishikawa, H., Tsuyama, N., Abroun, S., Liu, S., Li, F.J., Taniguchi, O., Kawano, M.M., 2002. Requirements of src family kinase activity associated with CD45 for myeloma cell proliferation by interleukin-6. *Blood* 99, 2172–2178.
- Judson, R., Houck, K., Martin, M., Richard, A.M., Knudsen, T.B., Shah, I., Little, S., Wambaugh, J., Woodrow Setzer, R., Kothiya, P., Phuong, J., Filer, D., Smith, D., Reif, D., Rotroff, D., Kleinstreuer, N., Sipes, N., Xia, M., Huang, R., Crofton, K., Thomas, R.S., 2016. Editor's Highlight: Analysis of the Effects of Cell Stress and Cytotoxicity on In Vitro Assay Activity Across a Diverse Chemical and Assay Space. *Toxicol. Sci.* 152, 323–339.
- Kim, S., Thiessen, P.A., Bolton, E.E., Chen, J., Fu, G., Gindulyte, A., Han, L., He, J., He, S., Shoemaker, B.A., Wang, J., Yu, B., Zhang, J., Bryant, S.H., 2016. PubChem substance and compound databases. *Nucleic Acids Res.* 44, D1202–D1213.
- Koopmans, F., van Nierop, P., Andres-Alonso, M., Byrnes, A., Cijssouw, T., Coba,

- M.P., Cornelisse, L.N., Farrell, R.J., Goldschmidt, H.L., Howrigan, D.P., Hussain, N.K., Imig, C., de Jong, A.P.H., Jung, H., Kohansalnodehi, M., Kramarz, B., Lipstein, N., Lovering, R.C., MacGillavry, H., Mariano, V., Mi, H., Ninov, M., Osumi-Sutherland, D., Pielot, R., Smalla, K.H., Tang, H., Tashman, K., Toonen, R.F.G., Verpelli, C., Reig-Viader, R., Watanabe, K., van Weering, J., Achsel, T., Ashrafi, G., Asi, N., Brown, T.C., De Camilli, P., Feuermann, M., Foulger, R.E., Gaudet, P., Joglekar, A., Kanellopoulos, A., Malenka, R., Nicoll, R.A., Pulido, C., de Juan-Sanz, J., Sheng, M., Südhof, T.C., Tilgner, H.U., Bagni, C., Bayés, À., Biederer, T., Brose, N., Chua, J.J.E., Dieterich, D.C., Gundelfinger, E.D., Hoogenraad, C., Hukanir, R.L., Jahn, R., Kaeser, P.S., Kim, E., Kreutz, M.R., McPherson, P.S., Neale, B.M., O'Connor, V., Posthuma, D., Ryan, T.A., Sala, C., Feng, G., Hyman, S.E., Thomas, P.D., Smit, A.B., Verhage, M., 2019. SynGO: An Evidence-Based, Expert-Curated Knowledge Base for the Synapse. *Neuron* 103, 217-234.e4.
- Krystal-Whittemore, M., Wen, H.Y., 2022. Update on HER2 expression in breast cancer. *Diagnostic Histopathol.* 28, 170–175.
- Kuhn, M., von Mering, C., Campillos, M., Jensen, L.J., Bork, P., 2008. STITCH: Interaction networks of chemicals and proteins. *Nucleic Acids Res.* 36, 684–688.
- Lang, J.Y., Hsu, J.L., Meric-Bernstam, F., Chang, C.J., Wang, Q., Bao, Y., Yamaguchi, H., Xie, X., Woodward, W.A., Yu, D., Hortobagyi, G.N., Hung, M.C., 2011. BikDD eliminates breast cancer initiating cells and synergizes with lapatinib for breast cancer treatment. *Cancer Cell* 20, 341–356.
- Lestari, I.A., Putra, I.M.R., Fatimah, N., Sri, N., Ujiantari, O., Dewi, D., Putri, P., Hermawan, A., 2024. Characterization of Potential Target Genes of Borneol in Increasing Trastuzumab Sensitivity in HER2 + Trastuzumab- Resistant Breast Cancer : Bioinformatics and In Vitro Studies 25, 1623–1634.
- Leto, S.M., Trusolino, L., 2014. Primary and acquired resistance to EGFR-targeted therapies in colorectal cancer: Impact on future treatment strategies. *J. Mol. Med.* 92, 709–722.
- Li, J., Yuan, J., Li, Y., Wang, Jian, Gong, D., Xie, Q., Ma, R., Wang, Jiajun, Ren, M., Lu, D., Xu, Z., 2022. d-Borneol enhances cisplatin sensitivity via p21/p27-mediated S-phase arrest and cell apoptosis in non-small cell lung cancer cells and a murine xenograft model. *Cell. Mol. Biol. Lett.* 27, 1–20.
- Li, X.K., Kobayashi, H., Holland, J.F., Ohnuma, T., 1993. Expression of dihydrofolate reductase and multidrug resistance genes in trimetrexate-resistant human leukemia cell lines. *Leuk. Res.* 17, 483–490.
- Lim, E.J., Kang, J.H., Kim, Y.J., Kim, S., Lee, S.J., 2022. ICAM-1 promotes cancer progression by regulating SRC activity as an adapter protein in colorectal cancer. *Cell Death Dis.* 13, 1–11.
- Liu, L., Zhong, L., Zhao, Y., Chen, M., Yao, S., Li, L., Xiao, C., Shan, Z., Gan, L., Xu, T., Liu, B., 2018. Effects of lapatinib on cell proliferation and apoptosis

- in NB4 cells. *Oncol. Lett.* 15, 235–242.
- Liu, R., Chen, Y., Liu, G., Li, C., Song, Y., Cao, Z., Li, W., Hu, J., Lu, C., Liu, Y., 2020. PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. *Cell Death Dis.* 11.
- Liu, T., Lin, Y., Wen, X., Jorissen, R.N., Gilson, M.K., 2007. BindingDB: A web-accessible database of experimentally determined protein-ligand binding affinities. *Nucleic Acids Res.* 35, 198–201.
- Ma, Y., Xia, Z., Ye, C., Lu, C., Zhou, S., Pan, J., Liu, C., Zhang, J., Liu, T., Hu, T., Xie, L., Wu, G., Zhao, Y., 2019. AGTR1 promotes lymph node metastasis in breast cancer by upregulating CXCR4/SDF-1 $\alpha$  and inducing cell migration and invasion. *Aging (Albany, NY)*. 11, 3969–3992.
- Malkas, L.H., Herbert, B.S., Abdel-Aziz, W., Dobrolecki, L.E., Liu, Y., Agarwal, B., Hoelz, D., Badve, S., Schnaper, L., Arnold, R.J., Mechref, Y., Novotny, M. V, Loehrer, P., Goulet, R.J., Hickey, R.J., 2006. A cancer-associated PCNA expressed in breast cancer has implications as a potential biomarker. *Proc. Natl. Acad. Sci. U. S. A.* 103, 19472–19477.
- McCubrey, J.A., Steelman, L.S., Bertrand, F.E., Davis, N.M., Abrams, S.L., Montalto, G., D’Assoro, A.B., Libra, M., Nicoletti, F., Maestro, R., Basecke, J., Cocco, L., Cervello, M., Martelli, A.M., 2014. Multifaceted roles of GSK-3 and Wnt/ $\beta$ -catenin in hematopoiesis and leukemogenesis: Opportunities for therapeutic intervention. *Leukemia* 28, 15–33.
- Mehta, P.K., Griendling, K.K., 2007. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. *Am. J. Physiol. - Cell Physiol.* 292, 82–97.
- Munagala, R., Aqil, F., Gupta, R.C., 2011. Promising molecular targeted therapies in breast cancer. *Indian J. Pharmacol.* 43, 236–245.
- Mura, G., Karaca Atabay, E., Menotti, M., Martinengo, C., Ambrogio, C., Giacomello, G., Arigoni, M., Olivero, M., Calogero, R.A., Chiarle, R., Voena, C., 2023. Regulation of CD45 phosphatase by oncogenic ALK in anaplastic large cell lymphoma. *Front. Oncol.* 12, 1–12.
- Naureen, I., Saleem, A., Aziz, M.K., Jam, A.H., Baneen, U., Chaudhary, A., Munir, S., Ahmed, I., 2022. Borneol as Adjuvant Chemotherapy: A New Way for the Development of Novel Chemotherapeutic. *Haya Saudi J. Life Sci.* 7, 128–141.
- Oh, E., Kim, J.Y., Cho, Y., An, H., Lee, N., Jo, H., Ban, C., Seo, J.H., 2016. Overexpression of angiotensin II type 1 receptor in breast cancer cells induces epithelial-mesenchymal transition and promotes tumor growth and angiogenesis. *Biochim. Biophys. Acta - Mol. Cell Res.* 1863, 1071–1081.
- Organista-Nava, J., Gómez-Gómez, Y., Illades-Aguilar, B., Rivera-Ramírez, A.B., Saavedra-Herrera, M.V., Leyva-Vázquez, M.A., 2018. Overexpression of dihydrofolate reductase is a factor of poor survival in acute lymphoblastic

leukemia. *Oncol. Lett.* 15, 8405–8411.

- Park, S.Y., Kwon, H.J., Choi, Y., Lee, H.E., Kim, S.W., Kim, J.H., Kim, I.A., Jung, N., Cho, N.Y., Kang, G.H., 2012. Distinct patterns of promoter CpG island methylation of breast cancer subtypes are associated with stem cell phenotypes. *Mod. Pathol.* 25, 185–196.
- Pasha, A., Kumar, K., Heena, S.K., Arnold Emerson, I., Pawar, S.C., 2024. Inhibition of NF- $\kappa$ B and COX-2 by andrographolide regulates the progression of cervical cancer by promoting PTEN expression and suppressing PI3K/AKT signalling pathway. *Sci. Rep.* 14, 1–22.
- Plesca, D., Mazumder, S., Almasan, A., 2008. DNA damage response and apoptosis. *Methods Enzymol.* 446, 107–122.
- Porcu, M., Kleppe, M., Gianfelici, V., Geerdens, E., De Keersmaecker, K., Tartaglia, M., Foà, R., Soulier, J., Cauwelier, B., Uyttebroeck, A., Macintyre, E., Vandenberghe, P., Asnafi, V., Cools, J., 2012. Mutation of the receptor tyrosine phosphatase PTPRC (CD45) in T-cell acute lymphoblastic leukemia. *Blood* 119, 4476–4479.
- Pozarowski, P., Darzynkiewicz, Z., 2004. Analysis of cell cycle by flow cytometry. *Methods Mol. Biol.* 281, 301–311.
- Qi, H.P., Gao, X.C., Zhang, L.Q., Wei, S.Q., Bi, S., Yang, Z.C., Cui, H., 2013. In vitro evaluation of enhancing effect of borneol on transcorneal permeation of compounds with different hydrophilicities and molecular sizes. *Eur. J. Pharmacol.* 705, 20–25.
- Quintayo, M.A., Munro, A.F., Thomas, J., Kunkler, I.H., Jack, W., Kerr, G.R., Dixon, J.M., Chetty, U., Bartlett, J.M.S., 2012. GSK3 $\beta$  and cyclin D1 expression predicts outcome in early breast cancer patients. *Breast Cancer Res. Treat.* 136, 161–168.
- Raiter, A., Zlotnik, O., Lipovetsky, J., Mugami, S., Dar, S., Lubin, I., Sharon, E., Cohen, C.J., Yerushalmi, R., 2021. A novel role for an old target: CD45 for breast cancer immunotherapy. *Oncoimmunology* 10, 1–14.
- Rhodes, D.R., Ateeq, B., Cao, Q., Tomlins, S.A., Mehra, R., Laxman, B., 2009. AGTR1 overexpression defines a subset of breast cancer and confers sensitivity to losartan, an AGTR1 antagonist 106.
- Rhodes, L. V, Short, S.P., Neel, N.F., Salvo, V.A., Zhu, Y., Elliott, S., Wei, Y., Yu, D., Sun, M., Muir, S.E., Fonseca, J.P., Bratton, M.R., Segar, C., Tilghman, S.L., Sobolik-Delmaire, T., Horton, L.W., Zaja-Milatovic, S., Collins-Burow, B.M., Wadsworth, S., Beckman, B.S., Wood, C.E., Fuqua, S.A., Nephew, K.P., Dent, P., Worthylake, R.A., Curiel, T.J., Hung, M.-C., Richmond, A., Burow, M.E., 2011. Cytokine receptor CXCR4 mediates estrogen-independent tumorigenesis, metastasis, and resistance to endocrine therapy in human breast cancer. *Cancer Res.* 71, 603–613.
- Sanz-Moreno, A., Palomeras, S., Pedersen, K., Morancho, B., Pascual, T., Galván,

- P., Benítez, S., Gomez-Miragaya, J., Ciscar, M., Jimenez, M., Pernas, S., Petit, A., Soler-Monsó, M.T., Viñas, G., Alsaleem, M., Rakha, E.A., Green, A.R., Santamaria, P.G., Mulder, C., Lemeer, S., Arribas, J., Prat, A., Puig, T., Gonzalez-Suarez, E., 2021. RANK signaling increases after anti-HER2 therapy contributing to the emergence of resistance in HER2-positive breast cancer. *Breast Cancer Res.* 23, 1–18.
- Sauvé, K., Lepage, J., Sanchez, M., Heveker, N., Tremblay, A., 2009. Positive feedback activation of estrogen receptors by the CXCL12-CXCR4 pathway. *Cancer Res.* 69, 5793–5800.
- Schlam, I., Tarantino, P., Tolaney, S.M., 2022. Overcoming Resistance to HER2-Directed Therapies in Breast Cancer. *Cancers (Basel)*. 14, 1–18.
- Shang, S., Hua, F., Hu, Z.W., 2017. The regulation of  $\beta$ -catenin activity and function in cancer: Therapeutic opportunities. *Oncotarget* 8, 33972–33989.
- Shi, Q., Yang, W., Ouyang, Y., Liu, Y., Cai, Z., 2025. CXCR4 promotes tumor stemness maintenance and CDK4/6 inhibitors resistance in ER-positive breast cancer. *Breast Cancer Res.* 27, 15.
- Singh, A., Nunes, J.J., Ateeq, B., 2015. Role and therapeutic potential of G-protein coupled receptors in breast cancer progression and metastases. *Eur. J. Pharmacol.* 763, 178–183.
- Skolastika, S., Hanif, N., Ikawati, M., Hermawan, A., 2022. Comprehensive Computational Analysis of Honokiol Targets for Cell Cycle Inhibition and Immunotherapy in Metastatic Breast Cancer Stem Cells. *Evidence-based Complement. Altern. Med.* 2022.
- Stelzer, G., Dalah, I., Stein, T.I., Satanower, Y., Rosen, N., Nativ, N., Oz-Levi, D., Olender, T., Belinky, F., Bahir, I., Krug, H., Perco, P., Mayer, B., Kolker, E., Safran, M., Lancet, D., 2011. In-silico human genomics with GeneCards. *Hum. Genomics* 5, 709–717.
- Stelzer, G., Rosen, N., Plaschkes, I., Zimmerman, S., Twik, M., Fishilevich, S., Iny Stein, T., Nudel, R., Lieder, I., Mazor, Y., Kaplan, S., Dahary, D., Warshawsky, D., Guan-Golan, Y., Kohn, A., Rappaport, N., Safran, M., Lancet, D., 2016. The GeneCards suite: From gene data mining to disease genome sequence analyses. *Curr. Protoc. Bioinforma.* 2016, 1.30.1-1.30.33.
- Tang, L., Wang, Y., Strom, A., Gustafsson, J.A., Guan, X., 2013. Lapatinib induces p27Kip1-dependent G1 arrest through both transcriptional and post-translational mechanisms. *Cell Cycle* 12, 2665–2674.
- Tapia Lopez, V.M., 2024. Early-onset breast cancer: a look from molecular biology. *Int. J. Mol. Biol. Open Access* 7, 35–39.
- Tomuleasa, C., Tigau, A.B., Munteanu, R., Moldovan, C.S., Kegyes, D., Onaciu, A., Gulei, D., Ghiaur, G., Einsele, H., Croce, C.M., 2024. Therapeutic advances of targeting receptor tyrosine kinases in cancer, *Signal Transduction and Targeted Therapy*. Springer US.

- Ugolkov, A., Gaisina, I., Zhang, J.S., Billadeau, D.D., White, K., Kozikowski, A., Jain, S., Cristofanilli, M., Giles, F., O'Halloran, T., Cryns, V.L., Mazar, A.P., 2016. GSK-3 inhibition overcomes chemoresistance in human breast cancer. *Cancer Lett.* 380, 384–392.
- van Driel, M.A., Brunner, H.G., 2006. Bioinformatics methods for identifying candidate disease genes. *Hum. Genomics* 2, 429–432.
- Wahdan-Alaswad, R., Liu, B., Thor, A.D., 2020. Targeted lapatinib anti-HER2/ErbB2 therapy resistance in breast cancer: opportunities to overcome a difficult problem. *Cancer Drug Resist.* 3, 179–198.
- Wan, Y., Liu, Jinxi, Mai, Y., Hong, Y., Jia, Z., Tian, G., Liu, Y., Liang, H., Liu, Jinghua, 2024. Current advances and future trends of hormesis in disease. *npj aging* 10, 26.
- Wang, M., Ding, L., Zhang, C., Yu, H., Ma, X., Wang, X., Zhong, F., Zhang, Q., 2023. Natural borneol serves as an adjuvant agent to promote the cellular uptake of piperlongumine for improving its antglioma efficacy. *Eur. J. Pharm. Sci.* 181, 106347.
- Wang, X., Wong, J., Sevinsky, C.J., Kokabee, L., Khan, F., Sun, Y., Conklin, D.S., 2016. Bruton's tyrosine kinase inhibitors prevent therapeutic escape in breast cancer cells. *Mol. Cancer Ther.* 15, 2198–2208.
- Wang, Z., Liang, L., Yin, Z., Lin, J., 2016. Improving chemical similarity ensemble approach in target prediction. *J. Cheminform.* 8, 1–11.
- Welsh, C.F., Roovers, K., Villanueva, J., Liu, Y., Schwartz, M.A., Assoian, R.K., 2001. Timing of cyclin D1 expression within G1 phase is controlled by Rho. *Nat. Cell Biol.* 3, 950–957.
- Witkiewicz, A.K., Cox, D., Knudsen, E.S., 2014. CDK4/6 inhibition provides a potent adjunct to Her2-targeted therapies in preclinical breast cancer models. *Genes and Cancer* 5, 261–272.
- Yang, S., Zeng, K., Luo, L., Qian, W., Wang, Z., Doležel, J., Zhang, M., Gao, X., Deng, Z., 2020. A flow cytometry-based analysis to establish a cell cycle synchronization protocol for *Saccharum* spp. *Sci. Rep.* 10, 5016.
- Yao, Z.J., Dong, J., Che, Y.J., Zhu, M.F., Wen, M., Wang, N.N., Wang, S., Lu, A.P., Cao, D.S., 2016. TargetNet: a web service for predicting potential drug–target interaction profiling via multi-target SAR models. *J. Comput. Aided. Mol. Des.* 30, 413–424.
- Ye, N., Cai, J., Dong, Y., Chen, H., Bo, Z., Zhao, X., Xia, M., Han, M., 2022. A multi-omic approach reveals utility of CD45 expression in prognosis and novel target discovery. *Front. Genet.* 13, 1–14.
- Yellapu, N.K., Ly, T., Sardi, M.E., Pei, D., Welch, D.R., Thompson, J.A., Koestler, D.C., 2022. Synergistic anti-proliferative activity of JQ1 and GSK2801 in triple-negative breast cancer. *BMC Cancer* 22, 1–21.

- Yoshitake, R., Saeki, K., Eto, S., Shinada, M., Nakano, R., Sugiya, H., Endo, Y., Fujita, N., Nishimura, R., Nakagawa, T., 2020. Aberrant expression of the COX2/PGE2 axis is induced by activation of the RAF/MEK/ERK pathway in BRAFV595E canine urothelial carcinoma. *Sci. Rep.* 10, 1–13.
- Zarzycka, M., Kotula-Balak, M., Gil, D., 2024. The mechanism of the contribution of ICAM-1 to epithelial–mesenchymal transition (EMT) in bladder cancer. *Hum. Cell* 37, 801–816.
- Zhang, M., Zheng, J., Nussinov, R., Ma, B., 2017. Release of Cytochrome C from Bax Pores at the Mitochondrial Membrane /631/114/2397 /639/638/440/56 /119/118 article. *Sci. Rep.* 7, 1–13.
- Zhang, R., Qiao, H., Chen, S., Chen, X., Dou, K., Wei, L., Zhang, J., 2016. Berberine reverses lapatinib resistance of HER2-positive breast cancer cells by increasing the level of ROS. *Cancer Biol. Ther.* 17, 925–934.
- Zi, D., Li, Q., Xu, C., Zhou, Z., Song, G., Hu, C., 2022. CXCR4 knockdown enhances sensitivity of paclitaxel via the PI3K / Akt / mTOR pathway in ovarian carcinoma 14, 4673–4698.