

References:

- [1] Patrick GL. An Introduction to Medicinal Chemistry. UCL Lect Notes 2009;40:752.
- [2] Society AC. Cancer Treatment. Cancer Treat Surviv Facts Fig 2013:44.
- [3] Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science* (80-) 1999;286:531–7.
- [4] Torpy JM. Cancer: The Basics. *JAMA J Am Med Assoc* 2010;304:1628.
- [5] Herbst RS, Heymach J V, Lippman SM. Lung cancer. *N Engl J Med* 2008;359:1367–80.
- [6] American Cancer Society. Cancer Facts & Figures 2016. *Cancer Facts Fig 2016* 2016:1–9.
- [7] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
- [8] Takiar R, Nadayil D, Nandakumar A. Projections of number of cancer cases in India (2010-2020) by cancer groups. *Asian Pacific J Cancer Prev* 2010;11:1045–9.
- [9] BioSpectrum. 1,300 Indians die of cancer every day: ICMR. *Biospectrum* 2015.
- [10] CRUK. Types of cells and cancer. *CancerHelp UK* 2013. <http://www.cancerresearchuk.org/cancer-help/about-cancer/what-is-cancer/cells/types-of-cells-and-cancer>.
- [11] Cancer Research UK. Surgery to treat cancer. *Cancer Treat* 2014.
- [12] Therapy R, Cdks B. The Science Behind Radiation Therapy. *Am Cancer Soc* 2014:15.
- [13] Couzin-Frankel J. Cancer Immunotherapy. *Science* (80-) 2013;342:1432–3.
- [14] Stokes Z, Chan S. Principles of cancer treatment by hormone therapy. *Surgery* 2009;27:165–8.
- [15] Beck B, Blanpain C. Unravelling cancer stem cell potential. *Nat Rev Cancer* 2013;13:727–38.
- [16] Friedman A a., Letai A, Fisher DE, Flaherty KT. Precision medicine for cancer with next-generation functional diagnostics. *Nat Rev Cancer* 2015;15:747–56.
- [17] Melero I, Berman DM, Aznar MA, Korman AJ, Gracia JLP, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer* 2015;15:457–72.

- [18] World Health Organization, Cancer Research UK. World cancer factsheet. World Health Organ 2014;2012:4.
- [19] Yarden Y, Shilo B-Z. SnapShot: EGFR signaling pathway. Cell 2007;131:1018.
- [20] Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001;37 Suppl 4:S9–15.
- [21] Kandasamy K, Mohan SS, Raju R, Keerthikumar S, Kumar GSS, Venugopal AK, et al. NetPath: a public resource of curated signal transduction pathways. Genome Biol 2010;11:R3.
- [22] Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, et al. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene 2006;366:2–16.
- [23] Olayioye M a, Neve RM, Lane H a, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. EMBO J 2000;19:3159–67.
- [24] Sebastian S, Settleman J, Reshkin SJ, Azzariti A, Bellizzi A, Paradiso A. The complexity of targeting EGFR signalling in cancer: From expression to turnover. Biochim Biophys Acta - Rev Cancer 2006;1766:120–39.
- [25] Batzer AG, Rotin D, Ureña JM, Skolnik EY, Schlessinger J. Hierarchy of binding sites for Grb2 and Shc on the epidermal growth factor receptor. Mol Cell Biol 1994;14:5192–201.
- [26] Dhillon a S, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene 2007;26:3279–90.
- [27] Anjum R, Blenis J. The RSK family of kinases: emerging roles in cellular signalling. Nat Rev Mol Cell Biol 2008;9:747–58.
- [28] Li J. PTEN, a Putative Protein Tyrosine Phosphatase Gene Mutated in Human Brain, Breast, and Prostate Cancer. Science (80-) 1997;275:1943–7.
- [29] Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. J Clin Oncol 2004;22:2954–63.
- [30] Sengupta S, Peterson TR, Sabatini DM. Regulation of the mTOR Complex 1 Pathway by Nutrients, Growth Factors, and Stress. Mol Cell 2010;40:310–22.
- [31] Carroll B, Maetzel D, Maddocks ODK, Otten G, Ratcliff M, Smith GR, et al. Control of TSC2-Rheb signaling axis by arginine regulates mTORC1 activity. Elife 2016;5.

- [32] Yano S, Kondo K, Yamaguchi M, Richmond G, Hutchison M, Wakeling A, et al. Distribution and Function of EGFR in Human Tissue and the Effect of EGFR Tyrosine Kinase Inhibition. *Anticancer Res* 2003;23:3639–50.
- [33] Albanell J, Gascón P. Small molecules with EGFR-TK inhibitor activity. *Curr Drug Targets* 2005;6:259–74.
- [34] Chong CR, Jänne P a. The quest to overcome resistance to EGFR-targeted therapies in cancer. *Nat Med* 2013;19:1389–400.
- [35] Antonicelli A, Cafarotti S, Indini A, Galli A, Russo A, Cesario A, et al. Egfr-targeted therapy for non-small cell lung cancer: Focus on EGFR oncogenic mutation. *Int J Med Sci* 2013;10:320–30.
- [36] Spano JP, Lagorce C, Atlan D, Milano G, Domont J, Benamouzig R, et al. Impact of EGFR expression on colorectal cancer patient prognosis and survival. *Ann Oncol* 2005;16:102–8.
- [37] Oliveira-Cunha M, Newman WG, Siriwardena AK. Epidermal growth factor receptor in pancreatic cancer. *Cancers (Basel)* 2011;3:1513–26.
- [38] Masuda H, Zhang D, Bartholomeusz C, Doihara H, Hortobagyi GN, Ueno NT. Role of epidermal growth factor receptor in breast cancer. *Breast Cancer Res Treat* 2012;136:331–45.
- [39] Kalyankrishna S, Grandis JR. Epidermal growth factor receptor biology in head and neck cancer. *J Clin Oncol* 2006;24:2666–72.
- [40] Chouaid C, Atsou K, Hejblum G, Vergnenegre A. Economics of treatments for non-small cell lung cancer. *Pharmacoeconomics* 2009;27:113–25.
- [41] Doss GPC, Rajith B, Chakraborty C, NagaSundaram N, Ali SK, Zhu H. Structural signature of the G719S-T790M double mutation in the EGFR kinase domain and its response to inhibitors. *Sci Rep* 2014;4:5868.
- [42] Steuer CE, Khuri FR, Ramalingam SS. The next generation of epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of lung cancer. *Cancer* 2015;121:E1–6.
- [43] Piotrowska Z, Niederst MJ, Karlovich CA, Wakelee HA, Neal JW, Mino-Kenudson M, et al.

- Heterogeneity underlies the emergence of EGFR^{T790} wild-type clones following treatment of T790M-positive cancers with a third-generation EGFR inhibitor. *Cancer Discov* 2015;5:713–23.
- [44] Nguyen K-SH, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. *Clin Lung Cancer* 2009;10:281–9.
- [45] Yasuda H, Park E, Yun C-H, Sng NJ, Lucena-Araujo AR, Yeo W-L, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med* 2013;5:216ra177.
- [46] Balak MN, Gong Y, Riely GJ, Somwar R, Li AR, Zakowski MF, et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin Cancer Res* 2006;12:6494–501.
- [47] Onitsuka T, Uramoto H, Nose N, Takenoyama M, Hanagiri T, Sugio K, et al. Acquired resistance to gefitinib: The contribution of mechanisms other than the T790M, MET, and HGF status. *Lung Cancer* 2010;68:198–203.
- [48] Costa DB, Halmos B, Kumar A, Schumer ST, Huberman MS, Boggan TJ, et al. BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. *PLoS Med* 2007;4:1669–80.
- [49] Song HN, Jung KS, Yoo KH, Cho J, Lee JY, Lim SH, et al. Acquired C797S mutation upon treatment with a T790M-specific third-generation EGFR inhibitor (HM61713) in non-small cell lung cancer. *J Thorac Oncol* 2016;11:e45–7.
- [50] Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK, Batra SK. Targeting the EGFR signaling pathway in cancer therapy. *Expert Opin Ther Targets* 2012;16:15–31.
- [51] Wu P, Nielsen TE, Clausen MH. Small-molecule kinase inhibitors: An analysis of FDA-approved drugs. *Drug Discov Today* 2016;21:5–10.
- [52] Yaish P, Gazit a, Gilon C, Levitzki a. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. *Science* (80-) 1988;242:933–5.
- [53] Finlay MR V, Anderton M, Ashton S, Ballard P, Bethel PA, Box MR, et al. Discovery of a

- potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem* 2014;57:8249–67.
- [54] Zhang L, Yang Y, Zhou H, Zheng Q, Li Y, Zheng S, et al. Structure-activity study of quinazoline derivatives leading to the discovery of potent EGFR-T790M inhibitors. *Eur J Med Chem* 2015;102:445–63.
- [55] Hu S, Xie G, Zhang DX, Davis C, Long W, Hu Y, et al. Synthesis and biological evaluation of crown ether fused quinazoline analogues as potent EGFR inhibitors. *Bioorganic Med Chem Lett* 2012;22:6301–5.
- [56] Cheng H, Nair SK, Murray BW, Almaden C, Bailey S, Baxi S, et al. Discovery of 1-((3R,4R)-3-((5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)methyl)-4-methoxypyrrolidin-1-yl)prop-2-en-1-one (PF-06459988), a Potent, WT Sparing, Irreversible Inhibitor of T790M-Containing EGFR Mutants. *J Med Chem* 2016;59:2005–24.
- [57] Sequist L V, Waltman B a, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
- [58] Walter AO, Sjin RTT, Haringsma HJ, Sun J, Ohashi K, Lee K, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M mediated resistance in NSCLC. *Cancer Discov* 2013;3:1404–15.
- [59] Minguet J, Smith KH, Bramlage P. Targeted therapies for treatment of non-small cell lung cancer - Recent advances and future perspectives. *Int J Cancer* 2016;138:2549–61.
- [60] Sequist L V, Soria J-C, Goldman JW, Wakelee H a, Gadgeel SM, Varga A, et al. Rociletinib in EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;372:1700–9.
- [61] Jia Y, Juarez J, Manuia M, Lelais G, Kasibhatla S, Long O, et al. Abstract 1734: In vitro characterization of EGF816, a third-generation mutant-selective EGFR inhibitor. *Cancer Res* 2014;74:1734–1734.
- [62] Kasibhatla S, Li J, Tompkins C, Vaillancourt M-T, Anderson J, Pferdekamper AC, et al. Abstract 1733: EGF816, a novel covalent inhibitor of mutant-selective epidermal growth factor receptor, overcomes T790M-mediated resistance in NSCLC. *Cancer Res*

- 2014;74:1733–1733.
- [63] Sakagami H, Konagai S, Yamamoto H, Tanaka H, Matsuya T, Mori M, et al. ASP8273, a novel mutant-selective irreversible EGFR inhibitor, inhibits growth of non-small cell lung cancer (NSCLC) cells with EGFR activating and T790M resistance mutations. *Cancer Res* 2014;74:#Abstr 1728.
- [64] Zhou W, Ercan D, Chen L, Yun CH, Li D, Capelletti M, et al. Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature* 2009;462:1070–4.
- [65] Lee et al KO. Discovery of HM61713 as an orally available and mutant EGFR selective inhibitor. *Cancer Res* 2014;74:#Abstr LB-100.
- [66] Ercan D, Choi HG, Yun C-H, Capelletti M, Xie T, Eck MJ, et al. EGFR mutations and resistance to Irreversible pyrimidine based EGFR inhibitors. *Clin Cancer Res* 2015:1078-0432.CCR-14-2789-.
- [67] Lee HJ, Schaefer G, Heffron TP, Shao L, Ye X, Sideris S, et al. Noncovalent wild-type-sparing inhibitors of EGFR T790M. *Cancer Discov* 2013;3:168–81.
- [68] Cheng H, Nair SK, Murray BW, Almaden C, Bailey S, Baxi S, et al. Discovery of 1-((3R,4R)-3-((5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)methyl)-4-methoxypyrrolidin-1-yl)prop-2-en-1-one (PF-06459988), a Potent, WT Sparing, Irreversible Inhibitor of T790M-Containing EGFR Mutants. *J Med Chem* 2016;59:2005–24.
- [69] Belani CP, Nemunaitis JJ, Chachoua A, Eisenberg PD, Raez LE, Cuevas JD, et al. Phase 2 trial of erlotinib with or without PF-3512676 (CPG 7909, a Toll-like receptor 9 agonist) in patients with advanced recurrent EGFR-positive non-small cell lung cancer. *Cancer Biol Ther* 2013;14:557–63.
- [70] Kaspersen SJ, Sørum C, Willassen V, Fuglseth E, Kjølbi E, Bjørkøy G, et al. Synthesis and in vitro EGFR (ErbB1) tyrosine kinase inhibitory activity of 4-N-substituted 6-aryl-7H-pyrrolo[2,3-d]pyrimidine-4-amines. *Eur J Med Chem* 2011;46:6002–14.
- [71] Thress KS, Paweletz CP, Felip E, Cho BC, Stetson D, Dougherty B, et al. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med* 2015;21:560–2.

- [72] Hu M, Ye W, Li J, Zhong G, He G, Xu Q, et al. Synthesis and Evaluation of Salicylanilide Derivatives as Potential Epidermal Growth Factor Receptor Inhibitors. *Chem Biol Drug Des* 2014;1–10.
- [73] Zhang Q, Diao Y, Wang F, Fu Y, Tang F, You Q, et al. Design and discovery of 4-anilinoquinazoline ureas as multikinase inhibitors targeting BRAF, VEGFR-2 and EGFR. *Medchemcomm* 2013;4:979.
- [74] Barbosa MLDC, Lima LM, Tesch R, Sant'Anna CMR, Totzke F, Kubbutat MHG, et al. Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors. *Eur J Med Chem* 2014;71:1–14.
- [75] Bugge S, Kaspersen SJ, Larsen S, Nonstad U, Bjørkøy G, Sundby E, et al. Structure-activity study leading to identification of a highly active thienopyrimidine based EGFR inhibitor. *Eur J Med Chem* 2014;75:354–74.
- [76] Ismail RSM, Ismail NSM, abuserii S, Abou El Ella DA. Recent advances in 4-aminoquinazoline based scaffold derivatives targeting EGFR kinases as anticancer agents. *Futur J Pharm Sci* 2016.
- [77] Yang M, Pickard AJ, Qiao X, Gueble MJ, Day CS, Kucera GL, et al. Synthesis, reactivity, and biological activity of gold(i) complexes modified with thiourea-functionalized tyrosine kinase inhibitors. *Inorg Chem* 2015;54:3316–24.
- [78] American Type Culture Collection. MTT Cell Proliferation Assay Instruction Guide. *Components* 2011;6597:1–6.
- [79] Chitkara D, Singh S, Kumar V, Danquah M, Behrman SW, Kumar N, et al. Micellar delivery of cyclophosphamide and gefitinib for treating pancreatic cancer. *Mol Pharm* 2012;9:2350–7.
- [80] Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J Med Chem* 2004;47:1739–49.
- [81] ChemAxon. Marvin Sketch. <https://www.chemaxon.com/products/marvin/> 2013.
- [82] Shelley JC, Cholletti A, Frye LL, Greenwood JR, Timlin MR, Uchimaya M. Epik: A software program for pKa prediction and protonation state generation for drug-like molecules. *J Comput Aided Mol Des* 2007;21:681–91.

- [83] Fernandes J, Gattass CR. Topological polar surface area defines substrate transport by multidrug resistance associated protein 1 (MRP1/ABCC1). *J Med Chem* 2009;52:1214–8.
- [84] Pollastri MP. Overview on the rule of five. *Curr Protoc Pharmacol* 2010.
- [85] Sander T, Freyss J, Von Korff M, Reich JR, Rufener C. OSIRIS, an entirely in-house developed drug discovery informatics system. *J Chem Inf Model* 2009;49:232–46.
- [86] Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. AdmetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *J Chem Inf Model* 2012;52:3099–105.
- [87] Meinel T, Ostermann C, Berthold MR. Maximum-score diversity selection for early drug discovery. *J Chem Inf Model* 2011;51:237–47.
- [88] Verdonk ML, Giangreco I, Hall RJ, Korb O, Mortenson PN, Murray CW. Docking performance of fragments and druglike compounds. *J Med Chem* 2011;54:5422–31.
- [89] Yun CH, Boggon TJ, Li Y, Woo MS, Greulich H, Meyerson M, et al. Structures of Lung Cancer-Derived EGFR Mutants and Inhibitor Complexes: Mechanism of Activation and Insights into Differential Inhibitor Sensitivity. *Cancer Cell* 2007;11:217–27.
- [90] Yurttaş L, Demirayak Ş, Ilgin S, Atli Ö. In vitro antitumor activity evaluation of some 1,2,4-triazine derivatives bearing piperazine amide moiety against breast cancer cells. *Bioorganic Med Chem* 2014;22:6313–23.
- [91] Promega. ADP-Glo™ Kinase Assay. *Luminescence* 2009:1–21.