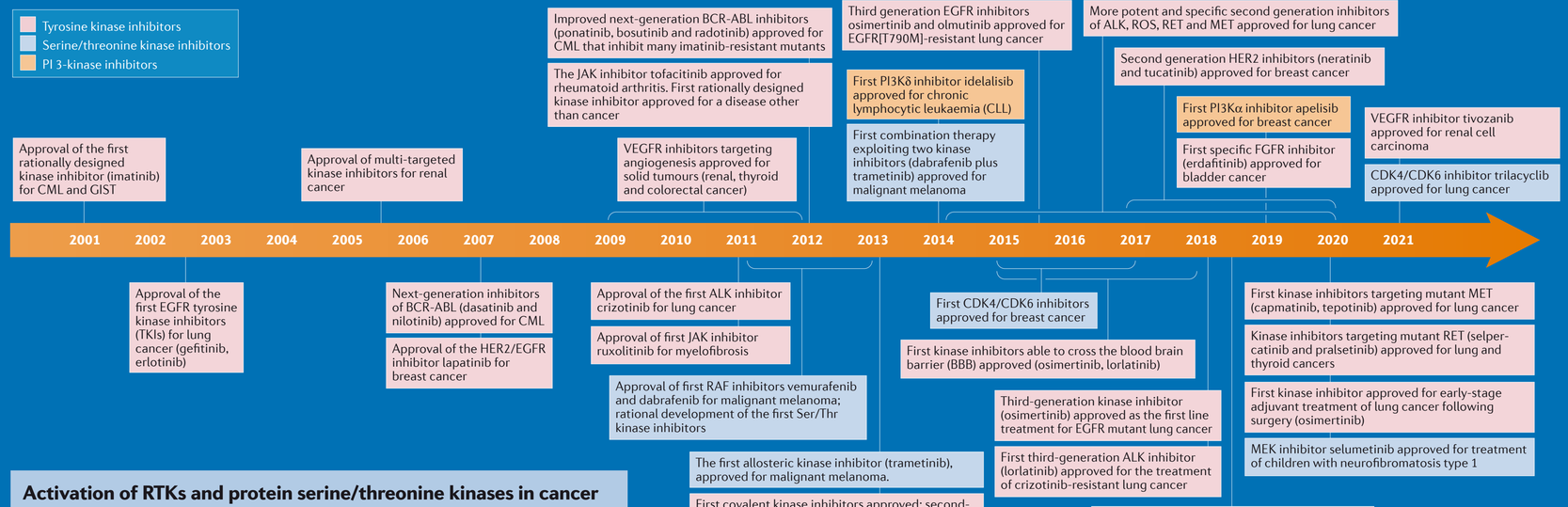
nature reviews drug discovery

Kinase drug discovery 20 years after imatinib

Philip Cohen[1], Darren Cross[2] and Pasi A. Jänne[3]

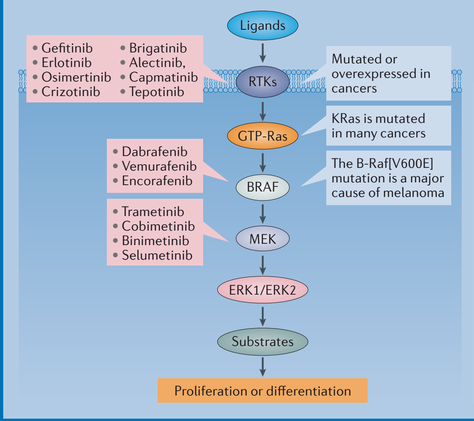
Protein kinases regulate nearly all aspects of cell life and alterations in their expression, or mutations in their genes, are implicated in various processes of carcinogenesis and pathologically involved in many other diseases, including autoimmune and inflammatory diseases, degenerative disorders and infectious diseases. Remarkable progress has been made over the past 20 years in improving the potency and specificity of small-molecule inhibitors of protein and lipid kinases and in addressing the challenge of drug resistance to kinase inhibitors. Together, such advances have culminated in the approval of more than 70 new drugs since imatinib was approved in 2001. These compounds have had a significant impact on the way in which we now treat various cancers as well as several non-cancerous conditions. (REFS 1–3)



Activation of RTKs and protein serine/threonine kinases in cancer

Receptor tyrosine kinases (RTKs) are cell surface receptors that bind and respond to growth factors to regulate cell growth, differentiation and survival. One of the most common intracellular signalling pathways triggered by RTKs is the mitogen-activated protein (MAP) kinase cascade. The MAP kinase cascade is frequently hyperactivated in lung and other cancers due to overexpression or mutation of RTKs (such as EGFR, ALK and MET) and downstream effectors (most commonly RAS and BRAF).

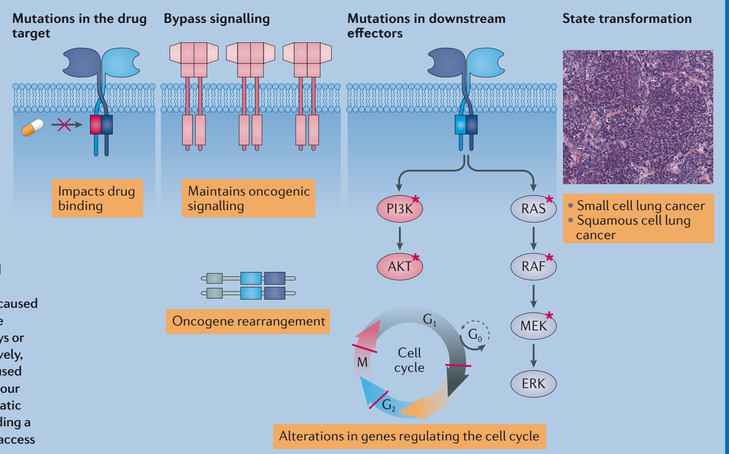
A number of drugs that target the RTKs EGFR, ALK and MET, as well as the downstream kinases BRAF and MEK, have gained approval. Activation of RTKs can also trigger activation of type 1 PI3K signalling, another intensive focus of drug discovery. Due to various challenges, including poor drug tolerance and drug resistance, only a small number of agents targeting PI3Ks are approved. (REFS 2, 4, 5)



The activation of RTKs triggers the conversion of the small guanine nucleotide-binding protein RAS from its inactive GDP-bound state into the active GTP-bound state. GTP–RAS then switches on the classical mitogen-activated protein (MAP) kinase pathway, a 'cascade' of protein serine/threonine kinases that activate each other sequentially.

Resistance to kinase inhibitors

Resistance to kinase inhibitors can be categorized as either innate/primary resistance or acquired resistance. Intrinsic resistance can be caused by tumours that harbour a population of cancer cells that are refractory to target inhibition from the outset owing to, for example, co-existing genetic aberrations in multiple oncogenic pathways. Acquired drug resistance is complex and the mechanisms are diverse, but they all result from cancer cells finding a route to maintain continued proliferative and survival signalling, despite the continued presence of the original kinase inhibitor. Acquired resistance mechanisms can be caused by on-target secondary mutations, by the acquisition of 'bypass' signalling pathways or by histological transformation. Alternatively, they can be tumour cell extrinsic and caused by an alteration in the biology of the tumour microenvironment, or result from metastatic tumour cells evading the inhibitor by finding a sanctuary that the inhibitor cannot gain access to, such as the CNS.

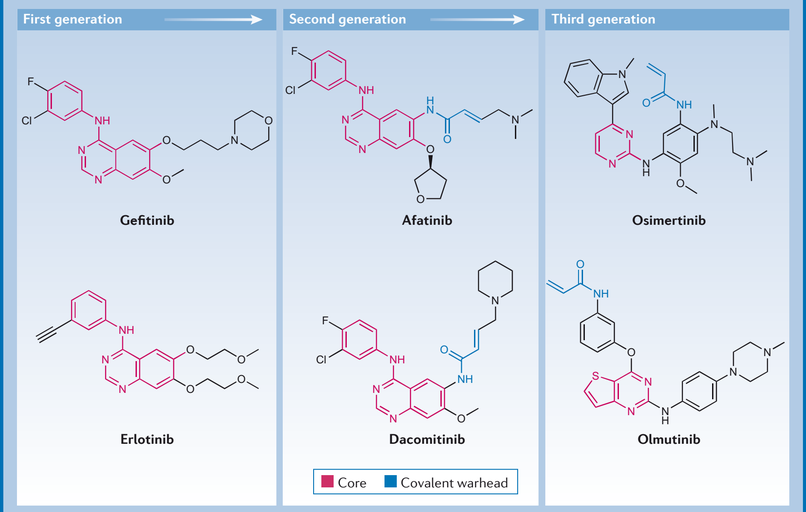


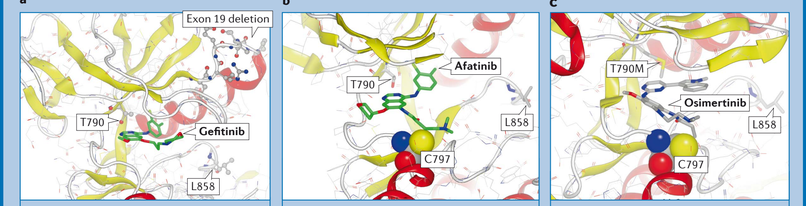
Next-generation drug development[2,6–8]

Guided by increased molecular and structural understanding of human kinases, the design of kinase inhibitors has been improved in multiple ways over the last 20 years. Approaches aimed at improving selectivity and overcoming the challenges of resistance encouraged a move away from ATP-competitive agents and a renewed interest in covalent inhibitors. EGFR kinase inhibitors are a key example of the theme of next- generation agent development to continuously improve drug properties.

The generation of kinase inhibitors that cross the blood–brain barrier (BBB) is becoming critical, because metastasis to the brain is now a common clinical issue that patients with advanced cancer are surviving for longer, and the brain is a sanctuary site for cancer cells that evade drug targeting. A deeper understanding of the properties a drug needs to cross the BBB and avoid efflux transporters is now resulting in the development and exploitation of increasing numbers of CNS-penetrant kinase inhibitors. (REFS 2, 9–12)

Despite these advances, acquired resistance to next-generation agents unfortunately still occurs, and new treatment approaches continue to be needed. One promising approach is the use of combination therapy that combines inhibitors of the original kinase mutation with inhibitors of a second kinase to block the predominant cause of resistance.





First-generation inhibitors have an anilinoquinazoline core backbone structure and bind reversibly in competition with ATP to potently inhibit EGFR catalytic activity.

Second-generation inhibitors share the quinazoline core structure, but contain a covalent warhead that enables irreversible binding, which increases potency but also increases toxicity. Afatinib forms a covalent bond with Cys797 of the EGFR.

Third-generation inhibitors overcome the EGFRT790M mutation. They contain a covalent warhead and a pyrimidine core backbone that is structurally distinct from the quinazoline-based structures. Osimertinib also forms a covalent bond with Cys797.

Abbreviations

AKT, protein serine threonine kinase encoded by the AKT gene, also called protein kinase B (PKB); ALK, anaplastic lymphoma kinase; BRAF, one of the three isoforms of the rapidly accelerated fibrosarcoma (RAF) serine/threonine protein kinase; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent protein kinase; CML, chronic myelogenous leukaemia; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase kinase; FGFR, fibroblast Growth Factor Receptor; GIST, gastro-intestinal-stromal tumour; HER2, human epidermal growth factor receptor 2; JAK, janus kinase; MEK, mitogen-activated protein kinase or extracellular signal-regulated or extracellular signal-regulated kinase; MET, MNNG HOS transforming gene tyrosine kinase; NTRK, neurotrophic tyrosine receptor kinase; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma, a protein serine/threonine kinase; RAS, a GTPase encoded by the RAS proto-oncogene; RET, receptor tyrosine kinase encodrd by the RET proto-oncogene; ROS, receptor tyrosine kinase encoded by the ROS proto-oncogene; VEGFR, vascular endothelial-derived growth factor receptor.

References

1. Cohen, P. Protein kinases — the major drug targets of the twenty-first century? *Nat. Rev. Drug Discov.* **1**, 309–315 (2002).
2. Cohen, P., Cross, D. R. & Janne, P. Kinase drug discovery 20 years after imatinib: progress and future directions. *Nat. Rev. Drug Discov.* **20**, 551–569 (2021).
3. Manning, G., Whyte, D. B., Martinez, R., Hunter, T. & Sudarsanam, S. The protein kinase complement of the human genome. *Science* **298**, 1912–1934, (2002).
4. Davies, H. et al. Mutations of the BRAF gene in human cancer. *Nature* **417**, 949–954 (2002).
5. Robert, C. et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N. Engl. J. Med.* **381**, 626–636 (2019).
6. Gorre, M. E. et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* **293**, 876–880 (2001).
7. Abdeldayem, A. et al. Advances in covalent kinase inhibitors. *Chem. Soc. Rev.* **49**, 2617–2687 (2020).
8. Liu, Q. et al. Developing irreversible inhibitors of the protein kinase cysteinome. *Chem. Biol.* **20**, 146–159 (2013).
9. Heffron, T. P. Challenges of developing small-molecule kinase inhibitors for brain tumors and the need for emphasis on free drug levels. *Neuro-oncology* **20**, 307–312 (2017).
10. Skerratt, S. E. & Storer, R. I. in Kinase Drug Discovery: *Modern Approaches* (eds Ward, R. A. & Goldberg, F. W.) 128–180 (RSC, 2019).
11. Johnson, T. W. et al. Discovery of PF-06463922, a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J. Med. Chem.* **57**, 4720–4744 (2014).
12. Zeng, Q. et al. Discovery and evaluation of clinical candidate AZD3759, a potent, oral active, central nervous system-penetrant, epidermal growth factor receptor tyrosine kinase inhibitor. *J. Med. Chem.* **58**, 8200–8215 (2015).

Affiliations

[1]MRC Protein Phosphorylation and Ubiquitylation Unit, School of Life Sciences, University of Dundee, Dundee, UK.
[2]AstraZeneca, Cambridge, UK.
[3]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA.

Competing interests statement

P.C. has shares in Alliance Pharma, AstraZeneca and GlaxoSmithKline and is a member of the Scientific Advisory Boards of Mission Therapeutics, Ubiquigent and Biocatalyst International. D.C. is an employee and shareholder of AstraZeneca. P.A.J. has received consulting fees from AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Takeda Oncology, ACEA Biosciences, Eli Lilly and Company, Araxes Pharma, Ignyta, Mirati Therapeutics, Novartis, Loxo Oncology, Daiichi Sankyo, Sanofi Oncology, Voronoi, SFJ Pharmaceuticals, Biocartis, Novartis Oncology, Nuvalent, Eisai, Bayer, Transcenta and Silicon Therapeutics; receives post-marketing royalties from DFCI-owned intellectual property on EGFR mutations licensed to LabCorp; has sponsored research agreements with AstraZeneca, Daiichi Sankyo, Puma Biotechnology, Boehringer-Ingelheim, Eli Lilly and Company, Revolution Medicines, and Astellas Pharma; and has stock ownership in Gatekeeper Pharmaceuticals.

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