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EDITED AND REVIEWED BY
Bruno Villoutreix,
Hôpital Robert Debré, France

*CORRESPONDENCE
Panupong Mahalapbutr,
panupma@kku.ac.th

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Editorial: Discovery of EGFR tyrosine kinase inhibitors for cancer treatment

Panupong Mahalapbutr[1]* and Thanyada Rungrotmongkol[2,3]

[1]Department of Biochemistry, Center for Translational Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, [2]Program in Bioinformatics and Computational Biology, Graduate School, Chulalongkorn University, Bangkok, Thailand, [3]Center of Excellence in Structural and Computational Biology, Department of Biochemistry, Faculty of Science, Chulalongkorn University, Bangkok, Thailand

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Editorial on the Research Topic
Discovery of EGFR tyrosine kinase inhibitors for cancer treatment

Tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have long been established as conventional approaches for the treatment of non-small cell lung cancer (NSCLC) patients. However, mutations involving EGFR exon20 insertion (EGFR ex20ins), accounting for 6%–12% of all EGFR mutations in NSCLC, typically exhibit resistance to reversible EGFR TKIs, e.g., gefitinib and erlotinib (Zhang et al.). Consequently, numerous research endeavors have been undertaken in recent years to explore novel and effective strategies for overcoming the resistance to TKIs caused by EGFR ex20ins mutations.

This Research Topic gathers various contributions that underscore the use of TKIs (limertinib, pyrotinib, and anlotinib) in treating diverse forms of cancer. Furthermore, a review detailing the design and development of coumarin-1,2,3-triazole hybrids as novel anticancer agents is also included in this Research Topic.

Yang et al. demonstrated that patients with NSCLC carrying EGFR A763_Y764insFQEA and D770delinsGY insertions (accounting for 3%–8% and 2.0%–4.8% of EGFR ex20ins in NSCLC) respond well to currently approved EGFR TKIs as opposed to those with the D770_N771insSVD and V769_D770insASV variants. Therefore, A763_Y764insFQEA and D770delinsGY are classified as active mutations within the diverse EGFR ex20ins subtypes, and patients with these mutations can be effectively treated with the appropriate EGFR TKIs. Furthermore, computational simulations revealed structural similarities between A763_Y764insFQEA and D770delinsGY mutants and the wild-type EGFR. However, the D770_N771insSVD and V769_D770insASV variants exhibited a rearrangement of the C-helix and phosphate-binding loop into the drug-binding pocket, resulting in significant steric hindrance and reduced affinity for currently approved EGFR TKIs.

Zhang et al. discovered that ASK120067 (limertinib) exhibited potent kinase inhibitory activity against EGFR ex20ins. In addition, ASK120067 demonstrated a dose-dependent suppression of EGFR phosphorylation and cell proliferation, leading to cell apoptosis in TKI-resistant EGFR ex20ins-dependent BaF3 cells with significantly greater efficacy compared to gefitinib and erlotinib. On top of that, oral administration of

ASK120067 led to a reduction in phospho-EGFR ex20ins levels and resulted in substantial tumor regression in an EGFR ex20ins BaF3 xenograft model. These findings underscore the pre-clinical anti-tumor effectiveness of ASK120067 in EGFR ex20ins models, emphasizing its potential value for treating NSCLC patients with EGFR ex20ins mutations.

Pyrotinib, a novel irreversible dual TKI targeting EGFR/HER2, has been reported to exhibit promising anticancer potential and acceptable tolerability in various phase II and phase III randomized clinical trials. However, there is limited real-world data on pyrotinib, particularly regarding outcomes in HER2-positive metastatic breast cancer (MBC). The investigation conducted by Zhang et al. demonstrated the equivalent clinical efficacy in HER2-positive MBC patients when compared to results from phase II and phase III clinical trials with pyrotinib. Additionally, promising outcomes were observed in patients with brain metastases.

Lin et al. reported the case of a 49-year-old woman with advanced cervical carcinoma who underwent second-line treatment with oral anlotinib (12 mg, days 1–14, every 21 days) and injectable tislelizumab (200 mg, day 1, every 21 days). Seven days after initiating anlotinib, she developed symptoms suggestive of posterior reversible encephalopathy syndrome (PRES). Discontinuation of anlotinib, along with supportive treatment, resulted in the restoration of her binocular vision. The Naranjo score (+5) categorized the causality of this reaction as probable, implying the likelihood that the event could be an adverse reaction to anlotinib.

In clinical practice, a diverse range of anticancer agents derived from natural, semi-synthetic, and synthetic origins is accessible. However, these agents commonly face challenges, such as side effects and drug resistance, making them insufficient in combating the disease. Coumarin, a bicyclic benzene-pyrone-fused structure, exhibits a wide spectrum of biological effects and exhibits potent anticancer effects on various cancer cell lines. Similarly, triazole, a nitrogen-containing heterocycle, displays notable pharmacological effects, including anticancer activities. As single-target drug therapies are insufficient for the treatment of cancer, the design of hybrid anticancer drugs holds the potential to create a therapeutic agent with a broader range of action. Various coumarin-1,2,3-triazole hybrids discussed in this review exhibit promising anticancer activities, with IC_{50} values comparable to standard clinical drugs against various cancer cell lines. The reported anticancer efficacy of these hybrids is attributed to the selective inhibition of various enzymes, such as EGFR, VEGFR-2, topoisomerase II, and CDK-2/cyclin A2. Several hybrids, notably **46**, **50**, **61**, and **65–68** highlighted in this review, present a significant opportunity for further exploration Mishra and Upadhyay.

We hope that this Research Topic will serve as a valuable reference for readers seeking insights into the current advancements in the field of targeted cancer therapy.

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Conflict of interest

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