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Digest paper

Recent progress on third generation covalent EGFR inhibitors

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ABSTRACT

First generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (gefitinib and erlotinib) demonstrate excellent clinical efficacy for NSCLC patients carrying EGFR oncogenic mutations (L858R, del exon 19 deletions between amino acids 746 and 750). Invariable, drug resistance occurs with around 60% of it driven by the EGFR-T790M gatekeeper mutation. To counter the T790M-dependent resistance, third generation covalent EGFR inhibitors have been developed with high potency toward T790M containing mutants and selectivity over WT EGFR. This review provides an overview of the third generation drugs currently in clinical trials and also encompasses novel methodologies developed to discover third generation covalent EGFR drugs.

Lung cancer is the leading cause of cancer-related death worldwide.[1] A subset of these patients harbor oncogenic mutations in the epidermal growth factor receptor (EGFR) which constitute 10–30% of the non-small cell lung cancer (NSCLC) population resulting in an estimated 100–200 thousand newly diagnosed cases per year globally. The two frequent and mutually-exclusive primary mutations are EGFR L858R and EGFR Del (exon 19 deletions between amino acids 746 and 750) which account for approximately 85% of all mutant EGFR NSCLC cases.[2] Patients with these somatic mutants can be treated with first generation EGFR kinase inhibitor drugs (gefitinib[3] and erlotinib[4]) (Fig. 1) which have excellent response rates and disease control for 11–14 months. Invariably, responsive patients develop resistance to these therapies with approximately 60% driven by a single second-site EGFR kinase domain mutation (gatekeeper residue, T790M) which restores constitutive EGFR dependent signaling.[5,6] The mechanism of T790M-derived resistance remains controversial but is believed to be from three contributions—(i) increased ATP binding affinity for T790M mutants, (ii) steric clash between Met790 gatekeeper side chain and the aniline moiety of first generation EGFR TKIs that binds in the kinase back-pocket, and (iii) altered catalytic domain conformational dynamics.[5,7] Taken together, there is an unmet medical need with an expectation that blocking signaling from the drug resistant form of EGFR is clinically effective.

Covalent inhibitors can have advantages over reversible compounds because they achieve complete and sustained target engagement in the presence of high intracellular concentrations of the competitive ligand (ATP) in the cells which requires the physical turnover of the targeted protein to restore inhibited signaling pathways.[8–12] Indeed, second generation, covalent inhibitors of EGFR (dacomitinib,[13] afatinib[14]) based on earlier studies of canertinib (CI-1033)[15] (Fig. 1) demonstrate increased cellular potency against EGFR oncogenic variants (e.g., EGFR-L858R/T790M). These compounds utilize an aniline moiety to bind in the back pocket, and the aniline moiety clashes with Met790 side chain thus making their EGFR-T790M activity less potent than their WT activity. A liability of the second generation of EGFR drugs is that they potently inhibit wild-type EGFR and cause epithelium-based toxicities such as rash and diarrhea which limit their clinical dose.

A third generation of EGFR TKI drugs is emerging with high potency against T790M-containing mutants and selectivity over WT EGFR. A wealth of preclinical studies has been reported and clinical findings are becoming available. The current review is designed to highlight the novel methodologies developed to enable discovery of the third generation EGFR drugs and provide an overview of those currently in clinical trials.

Inhibitor bound cocrystal structures: The development of third generation drugs has been facilitated by advances in EGFR structural insight. The first published crystal structure of EGFR T790M mutant is EGFR T790M bound with WZ4002,[16] determined at

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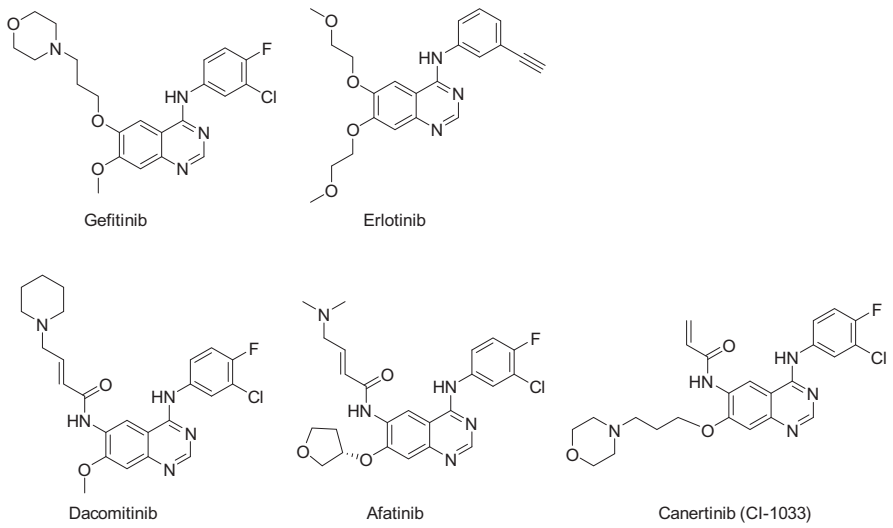

Figure 1. Summary of 1st generation and 2nd generation EGFR inhibitors.

2.9 Å resolution. The EGFR kinase domain is in the active conformation with the Asp855-Phe856-Gly857 (DFG) group at the base of the activation loop in a DFG-in conformation. As is illustrated in Figure 2, WZ4002 binds in the ATP binding pocket, forming the expected covalent bond with Cys 797. The anilinopyrimidine core of WZ4002 interacts with the hinge residue Met 793 by forming a bidentate hydrogen bonding interaction. The 5-Cl substituent on the pyrimidine ring forms hydrophobic interaction with the side chain of the gatekeeper residue Met790, which is hypothesized to provide a key contribution to the potency of WZ4002 against the EGFR T790M mutant. The aniline ring forms a hydrophobic interaction with the α-carbon of Gly 796 and its methoxy substituent extends towards Leu 792 and Pro 794 in the hinge region. At the Leu 792 position, JAK3 has a bulkier Tyr residue, and the remaining TEC family kinases have a bulkier Phe residue. When binding to other TEC family kinases, a steric clash would be expected between the methoxy group and the Tyr from JAK3 and Phe from the remaining TEC family kinases, therefore, WZ4002 exhibits selectivity against TEC family kinases.

The cocrystal structure of EGFR double mutant L858R/T790M bound with PF-06459988 (1.9 Å resolution), a potent irreversible inhibitor of EGFR L858R/T790M double mutant, was recently published.[17,18] The enzyme is in an unprecedented, hybrid conformation with the DFG motif oriented such that Phe 856 side chain is out of the hydrophobic core of the protein (DFG-out orientation) partially occupying the ATP binding site (Fig. 3). The Asp 855 side chain is positioned in the hydrophobic core. The rest of the activation loop has a conformation nearly identical to that in the active

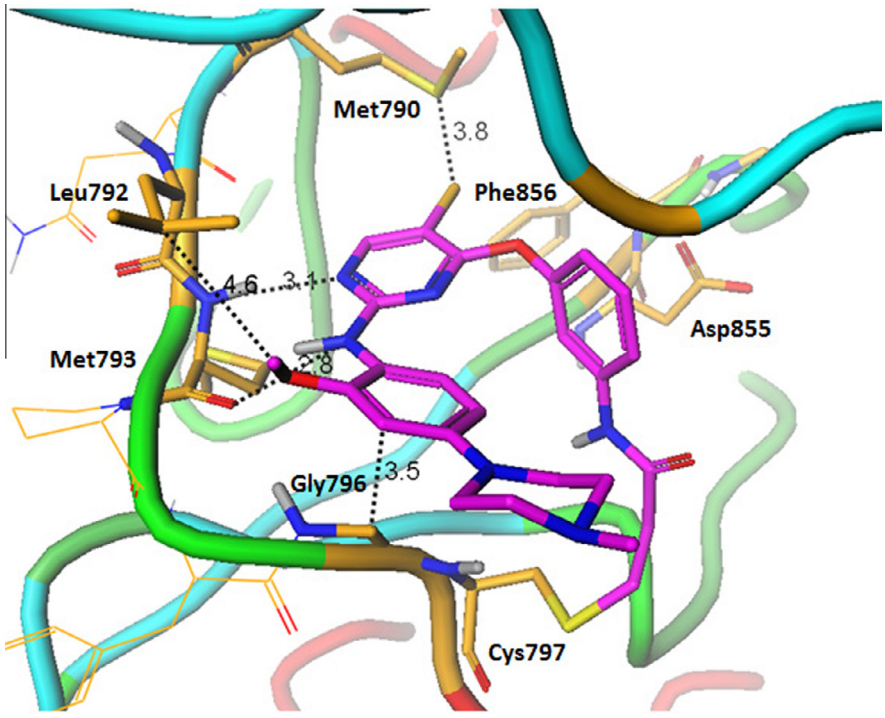

Figure 2. Cocrystal structure of EGFR T790M bound with WZ4002.