Docket #: S21-230

Potential Next-Generation Covalent EGFR Inhibitors

Researchers at Stanford have developed compounds for inhibiting the epidermal growth factor receptor (EGFR) that covalently label a nucleophile that has not been targeted before. This work could represent a next-generation EGFR inhibitor with potential to overcome resistance to the current therapy for EGFR-driven lung cancer and other diseases. Deregulation of EGFR – one of the most investigated receptor protein tyrosine kinases – has been implicated in many types of cancer, with overexpression present in at least 70% of human cancers including non-small lung cell carcinomas, breast cancers, gliomas, squamous cell carcinomas of the head and neck, and prostate cancer. EGFR has therefore emerged as an attractive target for developing diagnostic and therapeutic agents that can specifically bind and inhibit the receptor's tyrosine kinase activity and signal transduction pathway in cancer cells. EGFR's link to non-small-cell lung cancer (NSCLC) is well established; however, over 75% of patients die five years after their NSCLC diagnosis. Despite the success of some drugs, patients can acquire resistance through the acquisition of a mutation that precludes the ability of the drug to form essential covalent bonds. The need remains for potent small molecule EGFR inhibitors with alternative mechanisms of action targeting mutant EGFR.

Stage of Development
In vitro

Applications

- Potentially represents a next-generation EGFR inhibitor for treating kinase-mediated disorders including cancer and other proliferation diseases

Advantages

- High potential to overcome the resistance to current EGFR-target therapies, e.g., for lung cancer

Publications

- Li Z, Jiang J, Wang Y, Ficarro SB, Collins SJ, Beyett TS, Schaeffner IK, Tavares I, Gottlieb FH, Suda D, Gokhale PC, Black-Holmes LM, Gazgalis D, Eck MJ, Jänne PA, Marto JA, Che J, Gray NS, Zhang T. Overcoming EGFR resistance by monovalent and bident inhibitors targeting Cys775. *bioRxiv* [Preprint]. 2025 Dec 2:2025.11.28.691243. doi: 10.64898/2025.11.28.691243. PMID: 41573874; PMCID: PMC12822668.
- Li Z, Jiang J, Ficarro SB, Beyett TS, To C, Tavares I, Zhu Y, Li J, Eck MJ, Jänne PA, Marto JA, Zhang T, Che J, Gray NS. Molecular Bidents with Two Electrophilic Warheads as a New Pharmacological Modality. *ACS Cent Sci.* 2024 Feb 26;10(6):1156-1166. doi: 10.1021/acscentsci.3c01245. PMID: 38947214; PMCID: PMC11212140.

Patents

- Published Application: WO2023069959
- Published Application: 20240352021

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