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Therapeutic Strategy for EGFR-driven Cancers Using Macrocyclic Compounds

Researchers at Stanford have developed a novel method of using macrocyclic compounds that act as inhibitors of epidermal growth factor receptor (EGFR) for the treatment or prevention of kinase-mediated disorders, including cancer and other proliferation diseases.

EGFR is a receptor tyrosine kinase that regulates cell proliferation and survival in normal and malignant cells. Alterations in EGFR signaling are frequently found across human cancers, with elevated receptor expression reported in approximately 70% of cases. As a result, targeting EGFR has become central to the development of diagnostic and therapeutic agents that specifically inhibit its kinase activity. Tumors driven by activating mutations in the EGFR kinase domain initially respond to treatment with tyrosine kinase inhibitors (TKIs), however, resistance to therapy often arises due to a secondary T790M gatekeeper mutation. To address resistance to first-generation EGFR TKIs, irreversible T790M inhibitors were designed to covalently bind C797. Unfortunately, the emergence of a C797S mutation can block covalent binding, rendering the inhibitor ineffective and emphasizing the need for novel EGFR inhibitors with alternative mechanisms of action.

The laboratory of Dr. Gray has developed novel macrocyclic compounds capable of modulating the activity of EGFR (containing one or more mutations) by targeting Cys775. This approach represents a therapeutic strategy to prevent or treat various EGFR-driven tumors.

Stage of Development
proof of concept – in vitro data

Applications

- A method of inhibiting or decreasing the activity of EGFR in cells
- A kit with a compound capable of inhibiting EGFR activity, and instructions for use in treating cancer
- Therapeutic treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions

Advantages

- Compounds demonstrate greater inhibition of EGFR (containing one or more mutations) but do not affect the activity of a wild-type EGFR
- At least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, or 100-fold greater inhibition of EGFR relative to a wild-type EGFR

Innovators

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