Towards the Classification and Characterization of Epidermal Growth Factor Receptor (EGFR) Inhibitors

Henry Fuchs[1,2], Ross Giglio[3], Jośe McFaline-Figueroa[2]

[1] Yeshiva University; [2] Columbia University, Department of Biomedical Engineering; [3]Columbia University Irving Medical Center, Department of Molecular Pharmacology and Therapeutics

Introduction: One of the main contributors to the rapid proliferation of several forms of cancer (including glioblastoma, non-small lung cancer, and liver cancer) is dysregulation of the RTK/PI3K/MAPK kinase pathway, one example of this is caused by a mutation in EGFR. These findings led to the rapid development of many tyrosine kinase inhibitors and later several generations of EGFR specific inhibitors, many of which have shown promising results in treating these various cancers. [1]

In parallel, recent advances in high-throughput chemical transcriptomics have allowed us to study perturbation induced cell response at single cell resolution for a multitude of possible conditions. [2] While, these advances allow for the study of an unprecedented amount of data per experiment, it has led to a kind of "paradox of choice" in that it has become increasingly difficult to characterize and interpret said data due to its size and variation. In addition, while the size of the data has the promise of giving us greater confidence in choosing a direction for future study, it has become increasingly difficult to ascertain said direction due to these same factors. These considerations have garnered an interest in developing different classification and characterization techniques to better describe the perturbations themselves and the genetic responses of the cells to them.

Method: In our study we have implemented two modes of classification and characterization to a large screen of EGFR inhibitors (~ 600 drug/dose/batch conditions):

(1) An informed approach utilizing several common chemical and pharmacological annotations.
(2) An unbiased deep generative model, PerturbNet, which characterizes cell state shifts, attributes them to specific perturbation features, and designs idealized perturbations to a desired cell state shift. [3]

Results: Utilizing these two approaches we have found meaningful connections between canonical pharmaceutical classifications - i.e. reversibility - and perturbation signatures.

Discussion: While EGFR inhibitors all target the same protein, they result in varied transcriptomic responses. In establishing connections between these signatures and the drugs themselves via canonical classification or deep learning models, we can better understand the relationships between the two and hopefully begin to understand why some treatments are more successful than others, why some are effective in one cancer type but not in another, and much more.

Sources:

[1] Brennan et al. Cell 2013

[2] Srivatsan et al. Science 2020

[3] Yu et al. bioArxiv 2022

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