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

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Background:

- Mutated EGFR
- Identified in several cancer types, i.e. glioblastoma (~57%), non-small lung cancer (10%-35%), and more. [1] [2]

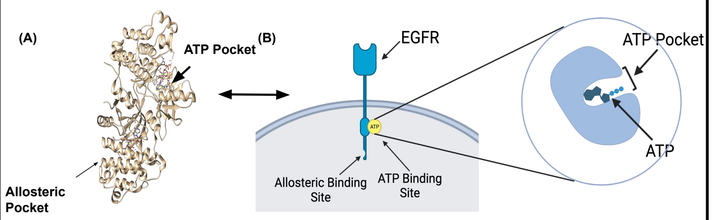


Fig. 1: (A) Protein Structure of EGFR (This visualization was made using the crystal structure with PDB code 5D41 by Chimera 1.17 on 21 July 2023) (B) Simplified visualization of EGFR.

- Over the past 20+ years pharmacologists have worked to develop EGFR inhibitors as a possible treatment for these cancer types. While several of these inhibitors have been shown to be effective against some cancer types, success against glioblastoma has remained elusive. [3]

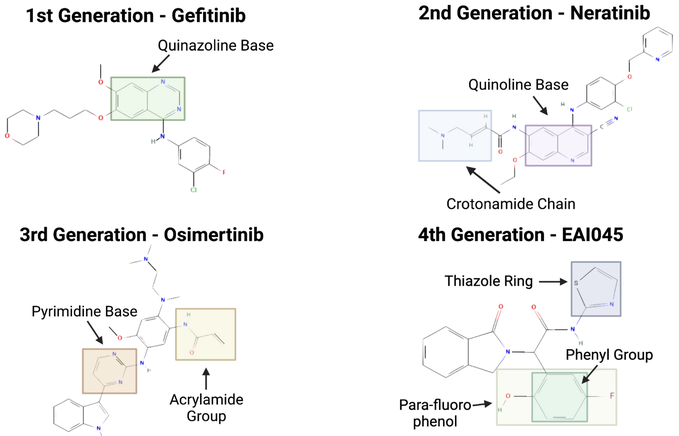


Fig. 2: Examples of each of the four generations, highlighting their defining chemical properties.

- With the advent of high-throughput chemical transcriptomics we now have the capacity to study many of these drugs in a single experiment, allowing us to see and analyze each of their individual genetic signatures. [4]

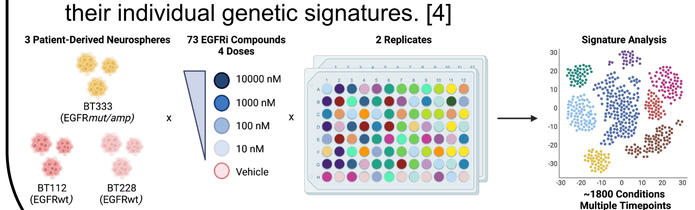


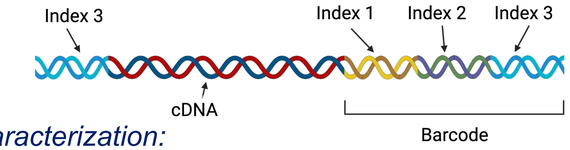
Fig. 3: Depiction of large screen workflow.

Method:

Building the Data Set:

SciPlex

- Plate based combinatorial indexing strategy for single cell RNA sequencing. [4]
- In out data set we are looking at **~80,000** cell transcriptomes across **~600** drug/dose/batch conditions.



Data Characterization:

Informed Approach: Chemical and Pharmaceutical Annotations

- Generation (see Fig. 2), Drug Class: (see Fig. 2), Binding Site: (see Fig. 1A), Reversibility, and Specificity.

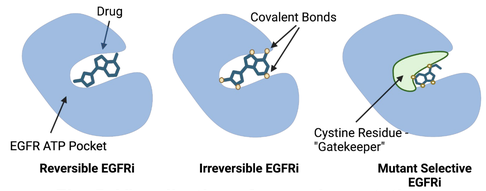
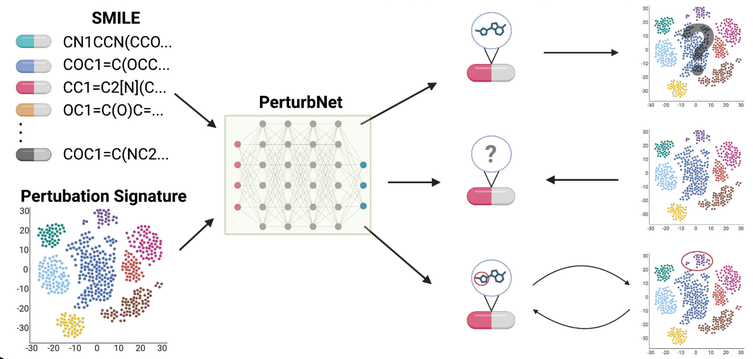


Fig. 5: Visualization of several annotations.

Unbiased Approach: PerturbNet [5] *(~ In Progress ~)*



Results:

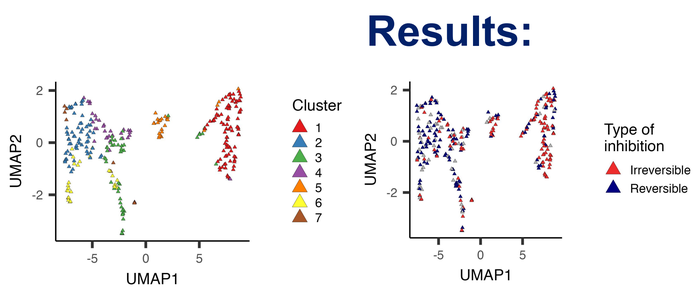
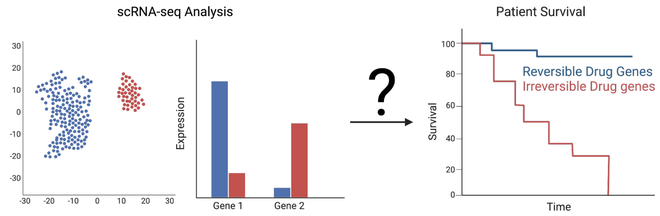


Fig. 6: Created with *Monocle3*

Discussion:

Local:

- EGFR inhibitors despite targeting the same protein, induce differential transcriptomic responses.
- By relating these differences to the chemical and pharmaceutical properties of the drugs we can gain further insight into understanding why there is such a lack of clinical success in Glioblastoma cases.



Global:

- Beyond glioblastoma, understanding the relationship between perturbations and their transcriptomic responses remains an elusive goal, by implementing deep learning models into our transcriptomics workflow we can establish relationships beyond that which can be achieved with canonical annotations.
- We recognize that transcriptomics and structural analysis (via SMILE) are just two subsets of perturbation analysis, however, the development of connections between all of the different subsets should lead to a far more robust understanding of perturbation response and drug development pipeline.

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References:

[1] Brennan et al. Cell 2013 **[2]** Li et al. Cell Commun Signal 2023

[3] Abourehab et al. Molecules 2021 **[4]** Srivatsan et al. Science 2020

[5] Yu et al. bioArxiv 2022

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