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Targeting Kinase Networks in Glioblastoma

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Targeting Kinase Networks in Glioblastoma

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Abstract

Glioblastoma (GBM) is one of the most invasive and deadliest of cancers and accounts for at least 50% of all primary tumors in the brain. It is a difficult disease to treat because of its invasive nature, heterogeneity, development of cell resistance to treatment, and because the selectivity of the blood-brain barrier allows very select few molecules into the brain.

The challenge is to design effective combination therapies for cancers, which is a difficult task to perform experimentally, because of the large number of such possible drug combinations.

We seek to target the network of kinases in GBM with 27 Blood Brain Barrier penetrant kinase inhibitors and analyze subsequent phosphoproteomic data. We seek to use the multiple off targets of kinase inhibitors to study the network effects of the drug rather than just a particular kinase. We plan to use Dynamic Modular Response, a mathematical model to analyze the various phosphoproteomic data obtained from GBM cell lines treated with Blood Brain Barrier penetrant Kinase Inhibitors, to build the network and predict drug combinations.

Motivation

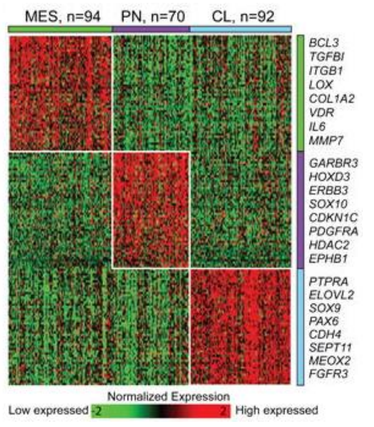


Figure 1: Signature gene cluster of three subtypes of GBM

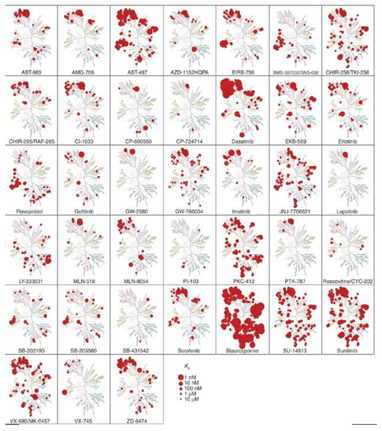


Figure 2: Kinase targets of different kinase inhibitors across the human kinome

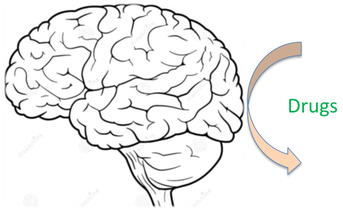
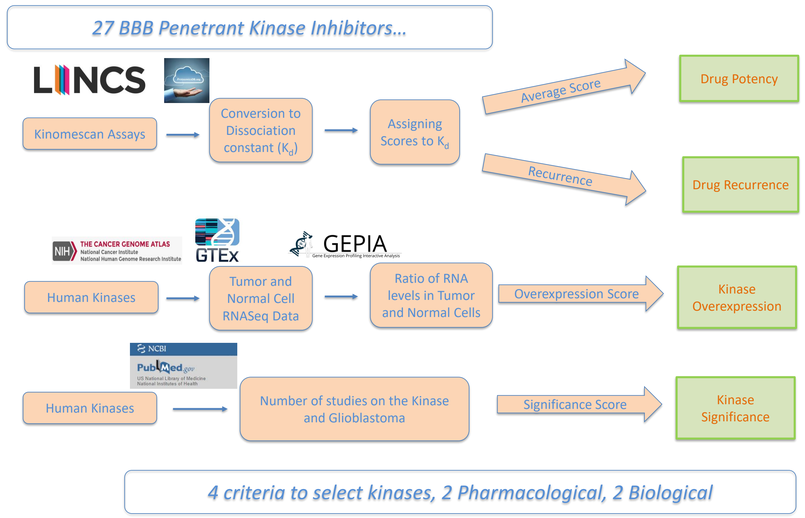


Figure 3: Tight junctions and gatekeeper proteins in the Blood Brain Barrier prevent most drugs from reaching the brain

Selection of relevant kinases in GBM



Dynamic Modular Response

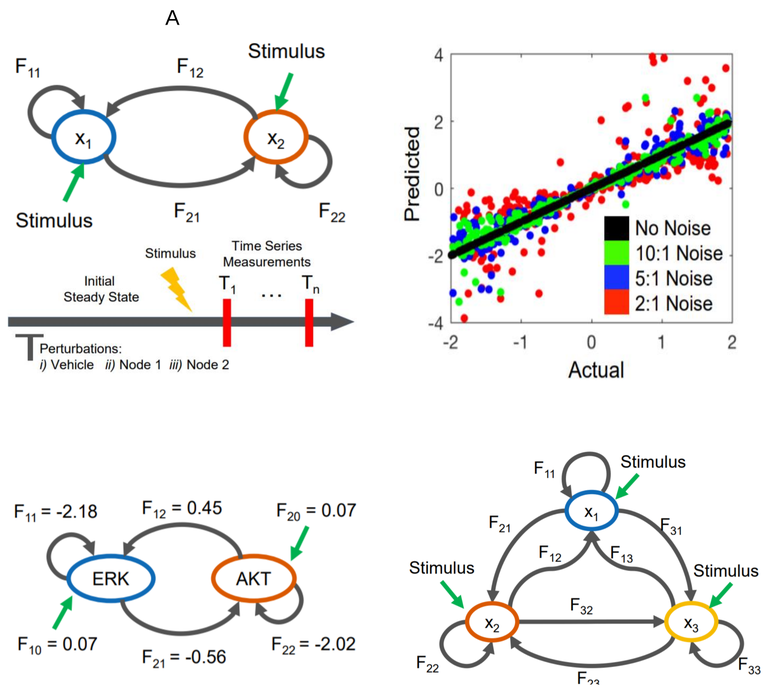
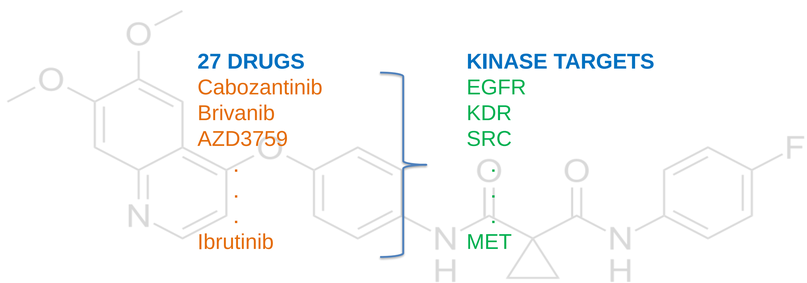


Figure 4: A. Perturbation of nodes and time course experiments to determine edge weights **B.** Predicted Edge weights vs Actual Edge weights for simulated experiments with 0, 0.1, 0.2 and 0.5 random noise **C.** Determining edge weights of ERK-AKT interaction in MCF10A cells under Insulin+ EGF stimulus. Perturbations used are MEK inhibition and AKT inhibition. **D.** Structure and interactions of a 3 node system

Looking Forward



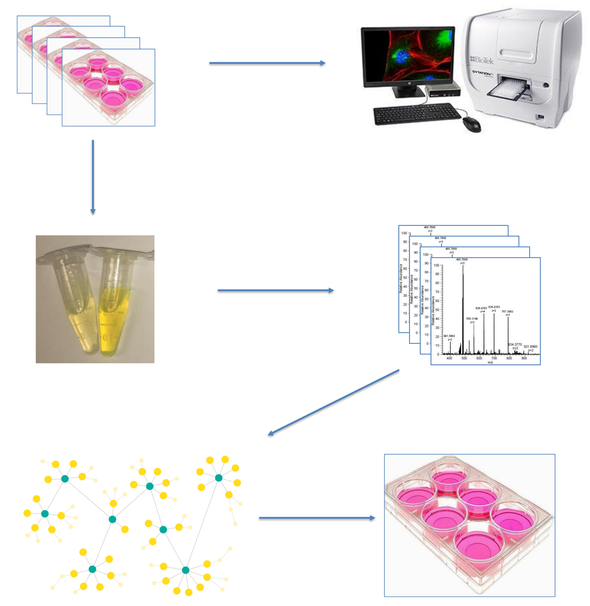


Figure 5: Experiments to determine network structure in GBM: A. List of Drugs and most important kinases in GBM determined through pharmacological and biological criteria. **B.** Cell culture of GBM cell lines treated with respective drugs **C.** Imaging of cells treated with different drugs to observe proliferation, movement and cell death **D.** Cell lysates of cells treated with different drugs for phosphoproteomic analysis **E.** Phosphoproteomic data for the relevant kinases in cells treated with multiple drugs **F.** Construction of kinase network **G.** Prediction and testing of drug combinations

Future Implications

This project should allow us to better rationalize combination therapy by better understanding how kinase drug targets are connected. If successful, we will lay a foundation for rational design of effective combination therapy not only for GBM but other cancer types.

Acknowledgements

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