Predicting cell phenotypes using signaling signatures

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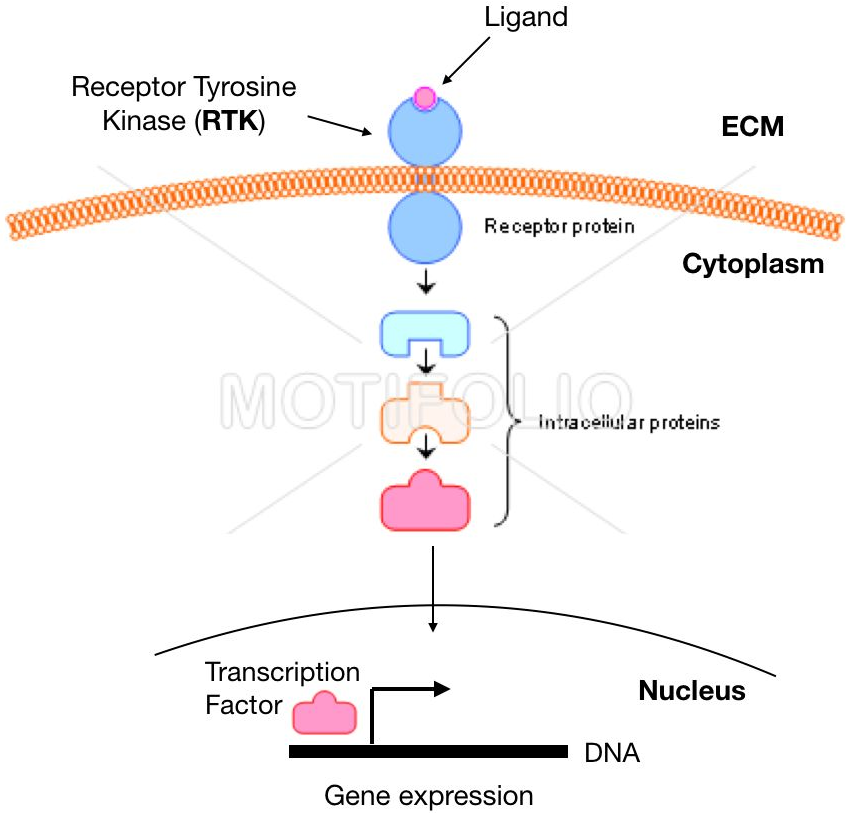
Protein kinases act as communicating nodes within *signaling pathways*

- Kinase-substrate interactions can swiftly switch “**on**” or “**off**” kinases forming accurate **signaling networks**
- Dysregulation of kinase function is demonstrated to be casually implicated in **disease**

Cell Decision Process
1. Environmental Signal
2. Signal Transduction
3. Cell response and phenotype



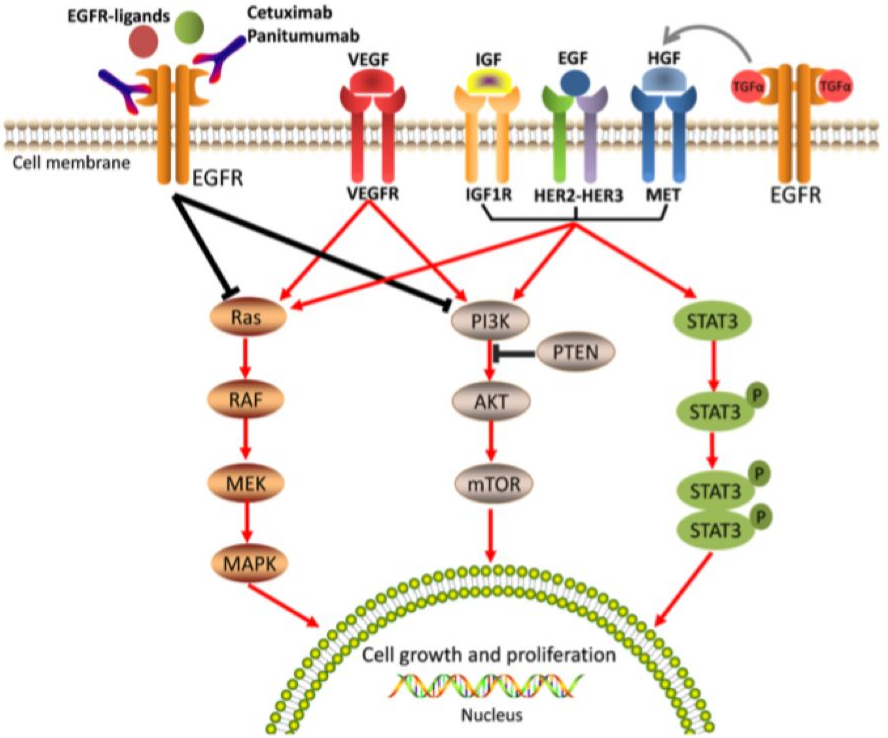
Background

Problem: Effectiveness of *targeted therapies* is limited by *Bypass Resistance* (BR)

- ➔ BR provides alternative activation routes and thus resistance
- ➔ BR can endow cells with new phenotypes

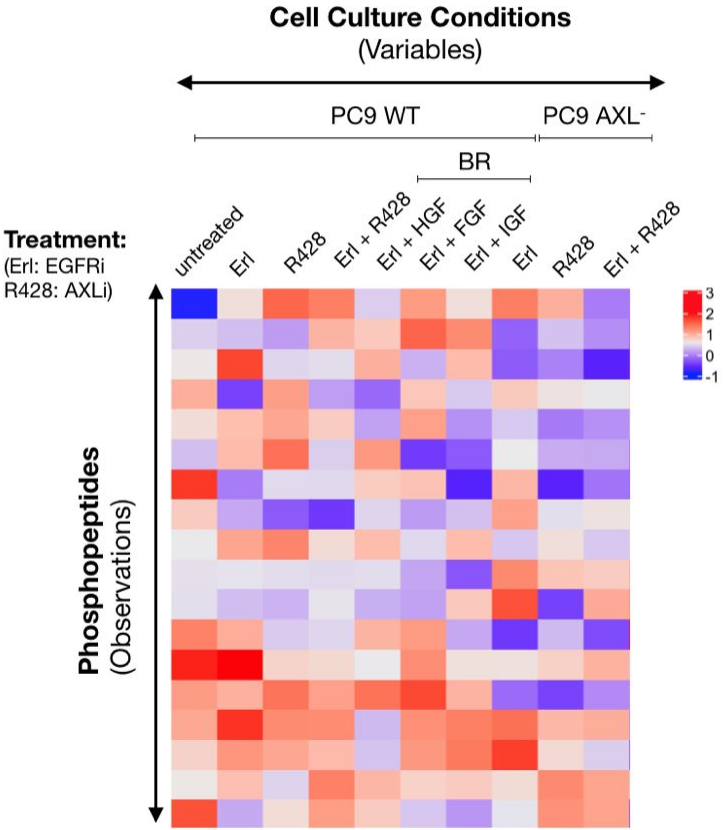
Receptor Tyrosine Kinase AXL:

- It has been reported to drive **resistance** to anti-EGFR therapies
- Epithelial-to-Mesenchymal Transition (MET), directs tumor **migration**
- Negative regulation on **inflammation**



Zhao et al. Oncotarget 2016

Data: *Signaling states* during switched RTK activation



- **Mass spectrometry** quantifies the phosphorylation status of signaling molecules

- Measurements are **normalized** to the untreated cell population

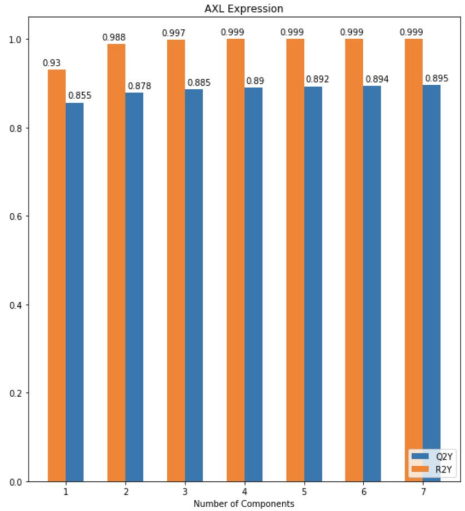
- **Solution**: *Regression* and *Clustering* analysis on this data set to identify the key signaling pathways triggering specific phenotypes. Our **Ys**:

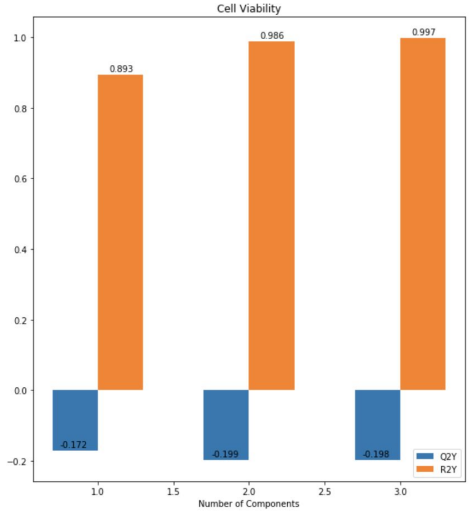
    A. Cell Viability
    B. AXL expression

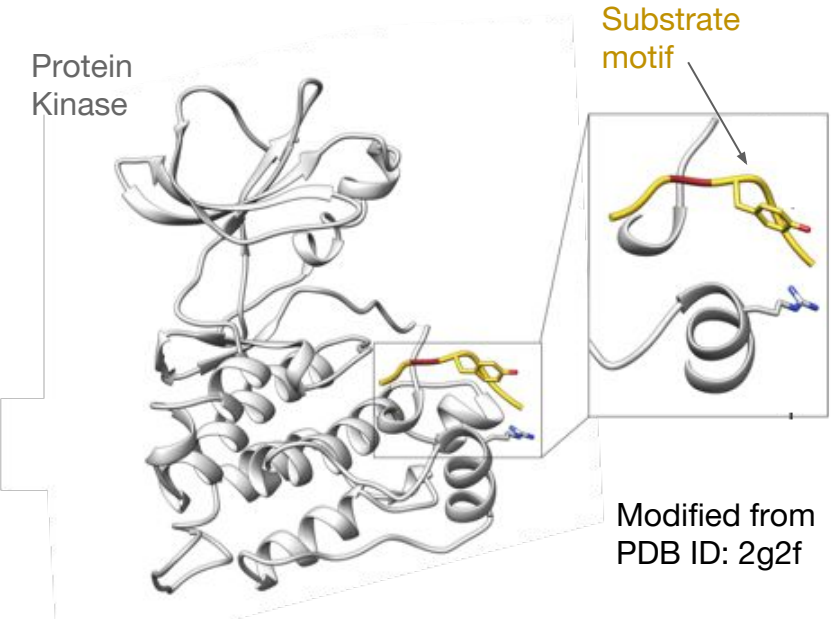
Model/Methods

PLSR:

- Fit separate PLSR models for measurements of both AXL expression and cell viability





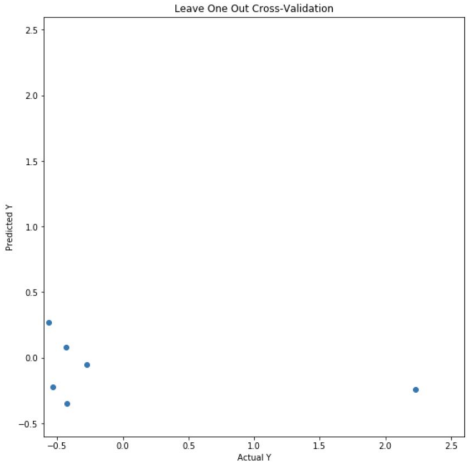


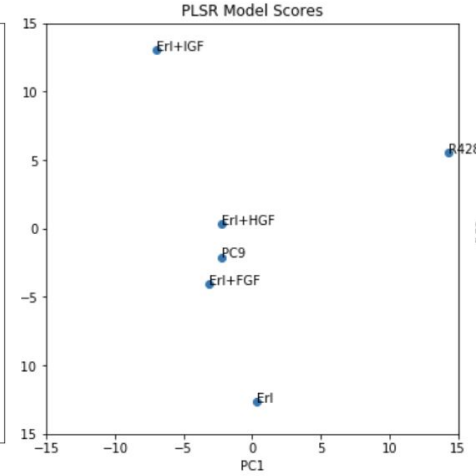
Clustering:

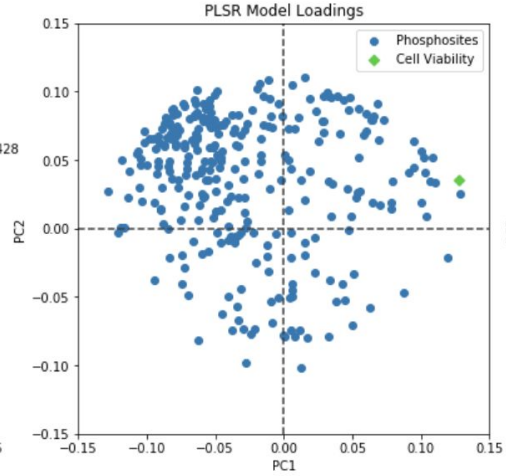
- Clustered phosphosite sequences using k-means according to Levenshtein distance
  - Using only 3 amino acids surrounding the phosphorylation site, as those are most correlated with kinase specificity
  - Previous clustering based on phosphorylation levels resulted in four distinct clusters

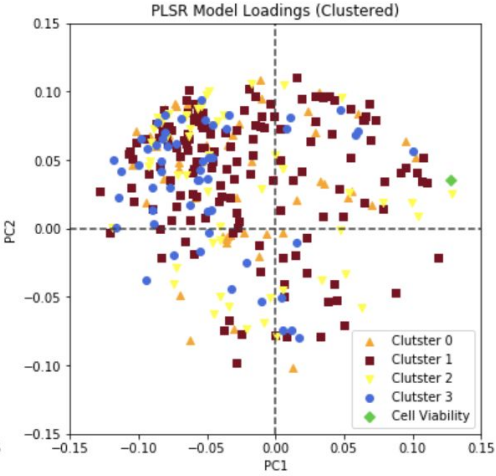
Model

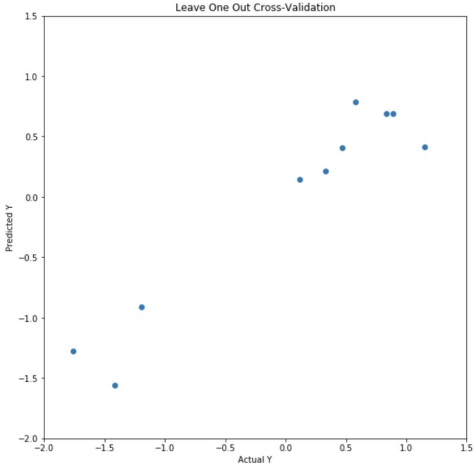
Results: Cell Viability (above) and AXL Expression (below)

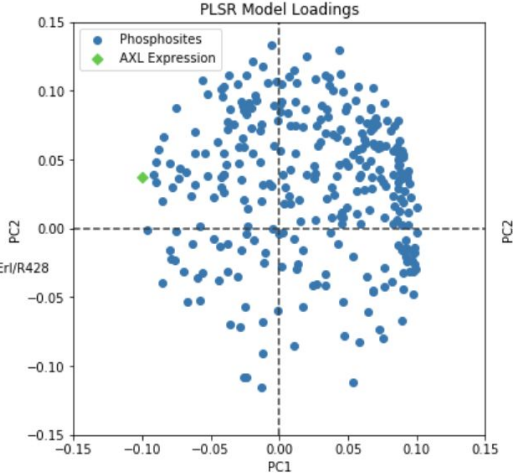


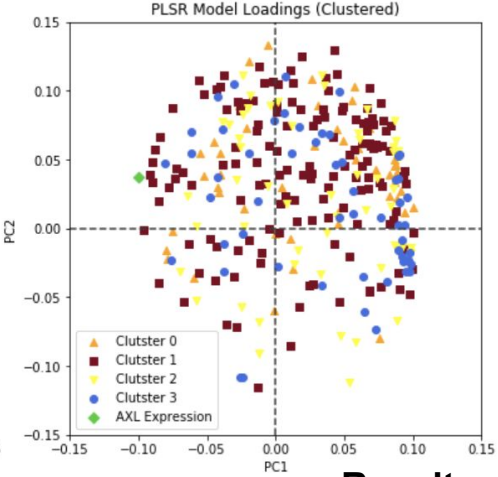












Conclusions

- *PLSR:*
  - Based on cross-validation, we do not consider either of the following models to be holistically predictive.

- *Clustering:*
  - With similar types of data, we hope to find a better-defined means of clustering.