**Combination Therapy in Melanoma: Finding Biomarkers of Synergistic Associations**

Large Scale Drug Combination Screening and Integrated Omics Data Analysis

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**Introduction**

The lack of complete response and the emergence of resistance in large numbers of patients are pushing clinicians to search for combination therapies to prevent disease progression. The ability to perform large scale omic analysis against a large number of drugs is an opportunity to develop a systematic approach for identifying optimal drug combinations in preclinical settings that can be further validated in clinical trials.

Prediction of synergy of drug combination usually involves measurements of single drug effects1,2 in comparison to the effect of the combination. The number of contexts (cell lines, etc.) is usually limited1,2. For each cell line, a heavy experimental workload is required1,4 to obtain dose-response curves and transcriptomics data in different pharmacological contexts. Thus, synergy prediction using data from multiple, untreated (e.g. without drug administration) cell lines or tumor samples is highly beneficial from a clinical point of view.

**1 Experimental workflow**

- 24 Melanoma cell lines
- 108 Drugs
- Low & high concentrations
- KEM® Platform

**2 Analysis workflow**

- Cell Lines omics data
- Markers associated with synergy?
- Association Rules

**Higher drug combinations**

- KEM BigData Rules management system

**3 Results**

10 Drug pairs experimentally tested (see)

**New drugs combinations**

- PLX4720 (Vemurafenib precursor)
- 104 Drug pairs
- Stringent filtering

**Synergistic VS non-synergistic**

- Genes differentially expressed (NES)
- 2509 rules

**References**


**Conclusion**

The complex problem of drug synergy prediction is tackled here in a systematic way. The KEM® BigData platform allows us to extract omics markers for numerous drug combinations through a highly scalable machine-learning approach. The process allowed us to identify common markers shared across multiple drug pairs as well as specific ones. Moreover, the analysis of results from existing clinical trials on formerly identified drug pairs strengthens our confidence in the candidate combinations identified as synergistic and not yet in clinical development.

Although molecular mechanisms driving synergy are still unclear, identification of synergistic drug pairs and associated specific biomarkers may be transformed in the future into a therapeutic decision support system, suggesting optimal combination therapies for melanoma patients.