

CASE STUDY

# Leveraging WES data to identify biomarker signatures



#### Client







## **Specification**

To identify biomarker signatures for efficacy/resistance to immunotherapy using gene expression profiles and somatic mutations in the Small Cell Carcinoma and Renal Cell Carcinoma patients.

## **Client challenges**

- Parameter optimization
- Running computationally intensive tools on XOP
- Extensive troubleshooting

# **Key activities**

## **Activity 1:**

Identification of biological themes for tumor and tumor microenvironment from gene expression profiles.

Building of gene expression networks using WGCNA and detecting co-expression modules Associating modules to clinical and other sample characteristics and perfrom enrichment analysis

Reduce the module of interest to signatures of biological significance

- WGCNA co-expression networks were constructed using multiple parameters, testing various sample and gene filtering criteria.
- The results from avelumab Javelin 101 RCC & avelumab Javelin 100 IL UC studies (Nature Medicine papers) were reproduced with the developed code.
- After validation of code by reproducing the results, boostrapped amalgamations of 1000 networks were generated (multiple times) to perform "consensus" network analysis and identify robust modules that could be repeatedly identified.
- Modules were annotated and correlated with clinical traits such as progression free and overall survival times.
- Gene set enrichment analysis was performed for modules using mSigDB collections.
- Reduced the module of interest to signatures using a combination of biological knowledge about pathways/ immune signatures as well as methods like elastic net.

### **Activity 2:**

Integration of mutation profiles with gene expression and identification of mechanisms for efficacy/resistance.

Identify somatic mutations with

Define pathways of interest in suffiecient details from review of part 1 results

based on co-expression information from

the patient expression profiles.

- functional impact from tumor only WES profiles Expression based stratification was done Paradigm-shift, DriverNet and DawnRank
- were used to understand impact of to identify differential profiles in the data. somatic mutations from the tumor whole Network topology was added using exome profiles alongside with baseline directed and undirected edges annotated transcriptomic profiles. in reactomoe/metabase for selected pathways. These were further augmented

Associate patient-wise pathway information to clinical covariates

 DawnRank analysis associated to responders and multiple therapies were done.

#### **Deliverables**

Analysis code in notebook format, network modules, gene signatures, augmented pathway definitions, and filtered functional mutations.

#### **Results**

- Developed an understanding of an approach to identify biomarker signatures within clinical data and related it to the IP of the client.
- Validated and optimized code was shared with the client.
- Network modules, gene signatures, augmented pathway definitions, and filtered functional mutations were shared from the analysis.